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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21876
Priority or Standard	Standard
Submit Date(s)	June 8, 2012
Received Date(s)	June 8, 2012
PDUFA Goal Date	April 8, 2013
Division / Office	Division of Reproductive and Urologic Products (DRUP)/Office of Drug Evaluation III (ODE III)
Reviewer Name(s)	Theresa H. van der Vlugt, M.D.
Review Completion Date	February 26, 2013
Established Name	Doxylamine Succinate plus Pyridoxine Hydrochloride
(Proposed) Trade Name	Diclegis
Therapeutic Class	Antihistamine plus Vitamin B_6 Analog
Applicant	OptumInsight for Duchesnay Inc.
Formulation(s)	Delayed Release Tablet
Dosing Regimen	Two Tablets at Bedtime, One Morning Tablet if Needed, One Mid-afternoon Tablet if Needed, Total of Four Oral Tablets Daily
Indication(s)	Treatment of Nausea and Vomiting of Pregnancy in Patients Who do not Respond to Conservative Management
Intended Population(s)	Pregnant Women

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of Diclegis® (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) delayed release Tablets, for oral use, in the treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management. Recommendation for approval is based on:

1. The safety and efficacy data presented in the Clinical Study Report for the single 15-day Phase 3 Study DIC-301 included in the application received on June 8, 2012.

   The safety of the Diclegis® delayed release Tablets is not a concern taken as follows: 2 tablets taken orally at bedtime to control nausea and vomiting of pregnancy occurring in the morning, additionally 1 tablet in the morning and 1 tablet in the mid-afternoon to control nausea and vomiting of pregnancy throughout the day (total of 4 delayed release tablets).

2. The safety and efficacy data for the reformulated Bendectin® (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) approved in 1976, as provided in this 505(b)(2) application. The original Bendectin® formulation was approved in 1956.

3. The Agency's reaffirmation of the safety of Bendectin. Bendectin® was voluntarily removed from the market by the manufacture Merrell Dow in 1983 because of financial considerations related to litigation and adverse publicity regarding an alleged linkage of the product to teratogenicity. The Agency determined on August 9, 1999, that the withdrawal of Bendectin® from sale was not for "reasons of safety or effectiveness". Even though Bendectin® was voluntarily removed from the market in 1983, the components of Bendectin®, doxylamine and vitamin B6, have continued to be consistently used off label in the practice of obstetrics for the treatment of nausea and vomiting of pregnancy not responsive to non-pharmacologic intervention.

   Additional data supporting the safety of the 505(b)(2) application for Diclegis® is provided in the Agency's August 9, 1999 determination that the Reference Listed Drug (RLD) Bendectin® was not removed from the market for "reasons of safety or effectiveness".

4. The safety data presented in the application for Diclectin® (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) manufactured by the Applicant Duchesnay Inc. in Canada since 1983.

No safety signals are seen in the Canadian postmarketing safety data for Diclectin®.

5. The 120-Day Safety Update Report received on October 5, 2012.

   The 120-Day Safety Update Report received on October 5, 2012 did not demonstrate any overall safety concerns for Diclegis®.

6. No outstanding issues remain from a Chemistry, Manufacturing and Controls (CMC) or nonclinical Pharmacology/Toxicology perspective.

1.2 Risk Benefit Assessment

The use of doxylamine succinate plus pyridoxine hydrochloride in combination as a treatment for nausea and vomiting of pregnancy has a long history. In 1956, the Food and Drug Administration (FDA) approved Bendectin® (10 mg doxylamine succinate, 10 mg pyridoxine hydrochloride, and 10 mg dicyclomine hydrochloride) delayed release Tablets for "nausea and vomiting of pregnancy which are unresponsive to conservative measures such as eating soda crackers or drinking hot and cold liquids, which interfere with normal eating habits or daily activities, and are sufficiently distressing to require drug intervention." Each Bendectin® tablet was formulated with (b) (4)

In 1976, Bendectin® was reformulated to include only 10 mg of doxylamine and 10 mg pyridoxine because the FDA Drug Efficacy Study Implementation (DESI) program determined that dicyclomine hydrochloride was ineffective for treating nausea and vomiting of pregnancy. The reformulated product, containing 10 mg of doxylamine succinate and 10 mg pyridoxine hydrochloride, was determined to be effective following the DESI review (Federal Register Notice, November 4, 1976).

Bendectin® was marketed in the U.S. from 1956 to 1983. On June 9, 1983, Bendectin® was withdrawn from the market for non-medical reasons, and has remained absent from the U.S. market since that time. On August 9, 1999, FDA made a determination that Bendectin® was indeed not withdrawn from sale for "reasons of safety or effectiveness".

No drug product is currently approved for the treatment of nausea and vomiting of pregnancy in the U.S.

In Canada, 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride are the ingredients in Diclectin® Tablets which is indicated for the management of nausea and vomiting of pregnancy (NVP). A product containing 10 mg doxylamine succinate and

10 mg pyridoxine hydrochloride for NVP has also been on the market in Spain since 1983.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarketing risk evaluation and mitigation strategies (REMS) are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarketing requirements and commitments are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

The drug product in the NDA application is a combination of 10 mg of doxylamine succinate and 10 mg of pyridoxine hydrochloride. (b) (4)

(b) (4)

In an August 3, 2012 submission, Duchesnay Inc. proposed the proprietary name Diclegis® (doxylamine succinate 10 mg and pyridoxine hydrochloride 10 mg) Delayed Release Tablets. On October 9, 2012, DMEPA advised Duchesnay, Inc. that the proposed proprietary name, Diclegis, was acceptable. "The proposed name, Diclegis, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you."

Hereafter in this review, the combination drug product containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride will be referred to as Diclegis.

Diclegis is a delayed release tablet containing 10 mg of doxylamine succinate (an antihistamine) and 10 mg of pyridoxine hydrochloride (vitamin B_6).

The proposed indication for Diclegis is for the treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management.

Duchesnay Inc. (hereafter referred to as Duchesnay) submitted NDA 21876 pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The Reference Listed Drug (RLD) is Bendectin® (NDA 10598). Bendectin® was withdrawn from the market in 1983 by the manufacturer for non-medical reasons. NDA 10598 was withdrawn by the manufacturer in February 2009.

No samples of the RLD were available for the purpose of conducting bioequivalence studies. Therefore, the Applicant conducted a single efficacy study (Phase 3 Study DIC-301).

2.2 Tables of Currently Available Treatments for Proposed Indications

There is no NDA approved and specifically labeled product available in the United States for the treatment of nausea and vomiting of pregnancy (NVP). Many treatment options for NVP have been described in the literature, however. Pyridoxine hydrochloride (vitamin B_6) or vitamin B_6 and doxylamine succinate is recognized as being "safe and effective" by the American College of Obstetricians and Gynecologists (ACOG) and is recommended as first-line pharmacotherapy.[1]

2.3 Availability of Proposed Active Ingredient in the United States

Doxylamine is primarily and widely used as the succinic acid salt, doxylamine succinate (hereafter referred to as doxylamine). Doxylamine is the sedating ingredient of NyQuil® (contains 6.25 mg doxylamine/15 mL), a common over the counter cold medication purchased in the United States. Doxylamine is also the active ingredient in the over-the-counter sleep-aid tablets branded as Unisom® (25 mg doxylamine). Antihistamines with sedating characteristics, such as doxylamine, are commonly used to treat nausea and vomiting of different causes.

Pyridoxine hydrochloride (hereafter referred to a pyridoxine) is a vitamin B_6 analog reported to have anti-nauseant activity. Pyridoxine is a prodrug that is metabolized to the biologically active metabolites: pyridoxal, pyridoxal 5'-phosphate, pyridoxamine and pyridoxamine 5'-phosphate. It is often used as the hydrochloride salt. Pyridoxine is

1 The American College of Obstetricians and Gynecologist. Nausea and Vomiting of Pregnancy. ACOG Practice Bulletin No.52. 2004;103(4):803-814.

available in oral supplements and injectable vitamins, and is used to correct vitamin B_6 deficiency. Pyridoxine is commonly available over the counter (preparations containing 25, 50, 100, 125, and 500 mg tablets and capsules), but is also found in prescription form (100 mg/mL injection).

Nausea and vomiting of pregnancy is a common condition that affects 70% to 85% of pregnant women.[2] About 50% of women have nausea and vomiting in early pregnancy, and an additional 25% have nausea alone. In about 35% of pregnant women who have this condition, nausea and vomiting are clinically significant, resulting in lost work time and negatively affecting family relationships.[3] According to Niebyl (2010), antiemetic agents should be prescribed in these patients when conservative measures, such as dietary and lifestyle modifications, have failed.

The etiology of NVP is unknown. Various theories have been proposed, however, including evolutionary adaptation[4] and hormonal stimulus[5].

In Canada, 10 mg doxylamine and 10 mg pyridoxine are the ingredients in Diclectin® which is indicated for the management of nausea and vomiting of pregnancy. In Europe, doxylamine is the active ingredient in the over-the-counter sleep-aid tablets branded as Sominex. A product named Cariban containing 10 mg doxylamine and 10 mg pyridoxine for nausea and vomiting of pregnancy has been on the market in Spain since 1983. A three component formulation containing 10 mg doxylamine succinate, 10 mg pyridoxine, and 10 mg dicyclomine for nausea and vomiting of pregnancy has been on the market in Portugal under the brand name Nausefe since 1976. In Commonwealth countries, such as Australia, South Africa and the United Kingdom, doxylamine is available in combination with acetaminophen and codeine as a treatment for tension headache and other types of pain, and is also used in over-the-counter sleep-aids.

2.4 Important Safety Issues With Consideration to Related Drugs

The use of doxylamine plus pyridoxine in combination as a treatment for nausea and vomiting of pregnancy has a long history. In 1956, the Food and Drug Administration (FDA) approved Bendectin® Delayed Release Tablets (doxylamine succinate, pyridoxine hydrochloride, and dicyclomine hydrochloride) manufactured by Hoechst Marion Roussel, Inc. (HMR) under NDA 10598 “only for nausea and vomiting of

2 Jewell D, Young G. Interventions for nausea and vomiting in early pregnancy (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.
3 Neibyl JR. Nausea and Vomiting in Pregnancy. N Engl J Med 2010;363:1544-50.
4 Flaxman SM, Sherman PW. Morning sickness: a mechanism for protecting mother and embryo. Q Rev Biol. 2000;75:113-148.
5 Yosimura M, Hershman JM. Thyrotropic action of human Chorionic gonadotropin. Thyroid. 1995;5:425-434.

pregnancy which are unresponsive to conservative measures such as eating soda crackers or drinking hot and cold liquids, which interfere with normal eating habits or daily activities, and are sufficiently distressing to require drug intervention." Each Bendectin® tablet was formulated with [redacted] (b) (4)

In 1976, Bendectin® was reformulated to include only 10 mg of doxylamine and 10 mg pyridoxine because the FDA Drug Efficacy Study Implementation (DESI) program determined that dicyclomine hydrochloride was ineffective for treating nausea and vomiting of pregnancy. The reformulated product, containing 10 mg of doxylamine succinate plus 10 mg pyridoxine hydrochloride, was determined to be effective following the DESI review.

Bendectin® was marketed in the U.S. from 1956 to 1983. On June 9, 1983, Merrell Dow (HMR's predecessor of interest) decided to cease manufacturing Bendectin® for non-medical reasons, citing litigation burdens and adverse publicity affecting Bendectin® (Bendectin® use was linked to teratogenicity in the public media). Bendectin® has remained absent from the U.S. market since 1983.

Other companies have continued to market versions of Bendectin® in other parts of the world. Duchesnay currently markets Diclectin® (10 mg of doxylamine succinate plus 10 mg pyridoxine hydrochloride) in Canada.

On October 20, 1997, Cato Research filed a citizen petition, under 21 CFR § 10.30, on behalf of Duchesnay (Docket No. 97P-0437/CPI), requesting that the FDA determine that Bendectin® was not withdrawn from sale for reasons of safety or effectiveness and to relist Bendectin® in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (commonly know as the "Orange Book").

On August 9, 1999, FDA made a determination that Bendectin® was indeed not withdrawn from sale for "reasons of safety and effectiveness".[6] Per the August 9, 1999 Federal Register Notice:

> "The agency's review of the withdrawal of Bendectin from the market has considered the sponsor's explanation of the basis for the withdrawal of the product in 1983 and information available to the agency regarding safety and effectiveness concerns for Bendectin. As noted previously, the sponsor has consistently maintained that it withdrew Bendectin from the market for reasons other the safety and effectiveness. The agency has reviewed information submitted with the petitions, published studies, U.S. and foreign adverse event reports, and FDA records. The current evidence

6 Federal Register/Vol. 64, No.152, August 9, 1999/Notices.

supports the conclusion that Bendectin was not withdrawn from the market for reasons of safety or effectiveness."

Bendectin® was relisted in the "Discontinued Drug Products List" section of the Orange Book. The "Discontinued Drug Product List" delineates, among other items, drug products that have been discontinued from marketing for reasons other then safety or effectiveness.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On April 18, 2005 Duchesnay submitted a 505(b)(2) NDA (NDA 10598) application for Diclegis for the indication (b) (4), citing Bendectin® as the RLD.

On June 16, 2005, the Division of Reproductive and Urologic Products (DRUP) sent a "refuse to file" letter to Duchesnay stating, "After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

- From a clinical pharmacology perspective, the 505(b)(2) application was not fileable because it did not contain information necessary to establish a link between the proposed formulation of (b) (4) and the Reference Listed Drug

(RLD), Bendectin. In the absence of adequate information to address this deficiency, reliance upon our finding of safety and efficacy for the RLD is not sufficient to support approval of [redacted] (b) (4)

- From a clinical perspective, the 505(b)(2) application is not fileable because the application is seeking an indication [redacted] (b) (4) For example, the proposed indication [redacted] (b) (4) is not supported by substantive data on safety and efficacy."

At a follow-up meeting conducted on August 9, 2005, DRUP provided Duchesnay the option of conducting an efficacy clinical trial (Phase 3 Study DIC-301) as a means of supplementing the application since there was no way of creating a bridge to the Bendectin® formulation. To address the issue of the proposed indication, Duchesnay revised the indication to read, "Treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management" based on DRUP's recommendation. DRUP provided Special Protocol Assessment comments to the draft protocol submitted initially on November 7, 2005 and revised on November 22, 2005.

The reported results of Phase 3 Study DIC-301 are included in this application.

2.6 Other Relevant Background Information

A Type C meeting was held on April 17, 2007 to review the 10 mg doxylamine succinate and 10 pyridoxine hydrochloride development program. Duchesnay informed DRUP that the two bioavailability studies (Study 02163 and Study 02191) submitted in the 2005 original NDA application had been independently audited based on the Division's concerns about the quality of data in studies performed at certain [redacted] (b) (4) [redacted] (b) (4). Bioanalytical work for both of these studies was conducted at one of the audited facilities: [redacted] (b) (4) As a result of the audit, data in at least one of the studies was considered unreliable. Based on these audit findings, Duchesnay proposed to conduct a new food effect study (Study 70294) and a new pharmacokinetic study (Study 70381) using the to-be marketed Diclegis formulation to provide additional support to the single efficacy Study DIC-301. DRUP agree to the proposal that bioavailability data from the studies at [redacted] (b) (4) be removed from the NDA application.

The safety and efficacy information that supports the application under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act is outlined in Table 1.

Table 1: Diclegis 505(b)(2) Source of Supporting Information

Source of Information	Information Provided
NDA 10598 Bendectin – FDA Determination of Safety	Nonclinical Toxicology
Published Literature	Nonclinical Toxicology
NDA 10598 Bendectin – FDA Determination of Efficacy	Clinical Efficacy
Diclegis Study DIC-301 Report	Clinical Efficacy
NDA 10598 Bendectin – FDA Determination of Safety	Clinical Safety
Published Literature	Clinical Safety
General Use of Active Ingredients in the U.S.	Clinical Safety
Postmarketing Experience with Diclectin® in Canada	Clinical Safety
NDA 10598 Bendectin	Labeling

Source: Adapted from NDA 21876, Clinical Overview, Table 2.5-2, page 12 of 61.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

At the request of Duchesnay, an independent audit was conducted by (b) (4) of the bioanalytical portions of two doxylamine/pyridoxine studies conducted at (b) (4) A complete (100%) review of raw data for the validations and associated bioequivalence studies were conducted. Per the 2007 audit report, "For study AA02268/BYY/BYZ, the data for doxylamine were found to be reliable. The data for pyridoxal were found to be marginal and the data for pyridoxine were found to be unreliable. The data for pyridoxal phosphate were also found to be reliable. Pyridoxamine and pyridoxamine phosphate levels were not quantifiable."

Per the application, "In light of an independent audit of the original bioavailability studies which cast some doubts on the dependability of the data from Study 02191", Studies 02191 and 02163 are considered supportive of safety only in the NDA application. The data from two new studies, Study 70294 (bioavailability) and Study 70381 (pharmacokinetics) are included in the application.

DRUP requested an inspection by the Office of Scientific Inspection (OSI) for the following clinical sites in the U.S. which participated in the single Phase 3 Study DIC-301:

1. Site # 20 for Study DIC-301; Stanley "Steve" Caritis, MD, Magee-Women's Hospital, Pittsburg, PA 15213.

2. Site # 11 for Study DIC-301; Gary Hankins, MD, University of Texas Medical Branch (UTMB) OB Regional Maternal Clinic, Pasadena, TX 77502.
3. Site # 30 for Study DIC-301; Menachen Miodovick, MD, Washington Hospital Center, Washington, DC 20010.

Medical Officer's Comments:

On November 30, 2012, OSI Division of Good Clinical Practice Compliance (DGCPC) brought an urgent issue to DRUP's attention regarding Site # 30 at the Washington Hospital Center. Per the information provided, "It appears that the research records were moved to a storage facility (b) (4) *the building's roof collapsed---."* (b) (4) *stored documents for Site # 30 at* (b) (4) *When* (b) (4) *requested the records for Site # 30 (13 cartons), they were advised that 10 of the 13 cartons were destroyed in the roof collapse. Likewise,* (b) (4) *was advised that all records (CRFs, ICFs, etc.) for Site # 31 (Dr. Menachen Miodovick, Georgetown Medical University) were also destroyed in the collapse.*

Per the information provided by DGCPC, complete records for 15 research subjects (out of 35 randomized subjects) were found following an initial review of the available boxes for Site # 30. The field investigator reviewed the retrievable data and was instructed to find any source records at Site # 30 to verify that all subjects existed. In addition, although Site # 31 (Georgetown Medical University) was not in DRUP's initial request, the inspection was expanded to this site to at least verify that source documents existed for all subjects at Site # 31.

Because of DGCPC's concern over the nature of the difficult inspection at Site # 30 (and Site # 31), DRUP agreed to expand the inspection to one additional site in Texas:

- *Site # 10 for Study DIC-301: Gary Hankins, MD; UTMB Regional Maternal & Child Health Program Clinic, Galveston, TX 77502.*

OSI responded on February 15, 2013. Per the Clinical Inspection Summary (CIS), at the conclusion of the inspection of Site # 20 (Dr. Steve Caritis), a Form FDA 483, Inspectional Observations, was issued. Dr. Caritis responded to the items listed on the Form FDA in a letter dated January 31, 2013 and outlined his commitment and specific actions for improving study practice to prevent such observations from occurring in future studies. The observations noted were:

1. In 7 of the 31 subject records reviewed, one or more of the required protocol procedures were not completed, for example, study completion visit completed 3 days outside the established window (Subject20-013), ultrasound performed 2 days outside the established window (Subject 20-023), Day 1 hematology (Subject 20-038) or urinalysis (Subject 20-025) not completed, Day 4 blood sample not taken

(Subject 20-052), Day 15 final study completion visit outside the established window (Subject 20-052), no documentation of the informed consent process (Subject 20-004), and physical exams not completed by the authorized study personnel (Subjects 20-037 and 20-032). Dr. Caritis agreed with these findings.

2. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.
   - Twenty-nine (29) of the 31 study records reviewed did not document if the subjects tried conservative therapies prior to enrollment. Dr. Caritis agreed that there was no documentation that subjects tried conservative therapies prior to enrollment.
   - Four (4) subjects reported active history of migraines (Subjects 20-009, 20-023, 20-025, and 20-032). Study records did not rule-out migraines as cause of NVP. Dr. Caritis disagreed, stating that women with nausea and vomiting associated with migraines present clinically different symptoms that NVP.
   - Absence of recorded concomitant medication use within 30 days prior to baseline, for example, B_6/Unisom use prescribed by private MD prior to study enrollment (Subjects 20-006, 20-007, and 20-032 with no documentation to confirm that the subject did or did not take medication), Compazine prescribed prior to study (Subject 20-036 without documentation of use), and Reglan anti-emetic use (Subject 20-071). Dr. Caritis agreed with these findings.

Per the CIS, the audit of Site # 20 "did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. However, the review division may wish to consider the impact, if any, regarding the fact that 29 of 31 study records reviewed do not document if the subjects tried conservative therapies prior to enrollment and the impact of the potential use of B_6/Unisom, Compazine, and Reglan in the subjects listed above. The other deviations noted appear to be isolated in nature and are unlikely to significantly impact safety of efficacy analyses." "With the exception of issues noted above, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication." "An inspection summary addendum will be generated if conclusions change upon receipt and review of the gathered evidence package."

Medical Officer's Comments:

Ideally, the information regarding conservative therapies for NVP prior to enrollment should have been collected in order to provide additional information on the success or failure of conservative therapies. Nonetheless, this reviewer believes that the absence of this information does not adversely impact the primary study endpoint of the mean change in the PUQE score between Baseline and Day 15. Each subject had to have a PUQE score ≥ 6 prior to enrollment confirming her degree of severity of NVP in spite of any conservative therapies she may have undertaken prior to study enrollment.

The 3 subjects who may or may not have used Unisom and the single subject each who may or may not have used Compazine or Reglan within 30 days prior to enrollment do not raise concerns for this reviewer. Two of these 5 subjects were not enrolled into Study DIC-301 (Subjects 20-007 and 20-032). The remaining 3 subjects completed Study DIC-301.

No addendum to the Establishment Inspection Report (EIR) was received as of the date of this review for Site # 20.

At the conclusion of the inspection of Dr. Gary Hankins at Site # 10 (Galveston, TX) and Site # 11 (Pasadena, TX), a Form FDA 483, Inspectional Observations, was issued. The observations noted were:

1. There was no documentation that the informed consent was signed prior to study procedures for Subjects 11-001, 11-017, 10-001, and 10-029.
2. The following subjects met the exclusion criteria and completed the study:
   - Subject 10-010 = ultrasound was 2 weeks outside the inclusion criteria of 7 -14 weeks gestation.
   - Subject 10-023 was taking Celexa (citalapram), and SSRI, for a history of depression.
   - Subject 10-029 was taking OTC Allegra-D, an antihistamine, at enrollment.

Per the CIS, "Data from these two sites are acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR and the gathered evidence package."

Medical Officer's Comments:

The above noted observations for the two Texas sites do not raise safety or efficacy concerns for this reviewer. These three subjects completed the study without the occurrence of a serious adverse event.

No addendum to the Establishment Inspection Report (EIR) was received as of the date of this review for Sites # 10 and # 11.

As noted previously, only a limited number of records were available for review at Site # 30 and Site # 31 (Dr. Menachem Miodovnik) due to destroyed records following a roof collapse at the building were the records were being stored. Therefore, a review of the informed consent and verification of source documents for screening and visit data were only done for the following subjects at Site # 30: Subjects 30-001 through 30-007, Subjects 30-021 through 30-026, Subject 30-034 and Subject 30-035. All case report forms, informed consent documents and regulatory binders for Site # 31 (Georgetown Medical University) were destroyed in the roof collapse.

Per the CIS, at the conclusion of the inspection of Site # 30, a Form FDA 483, Inspectional Observations, was issued. The observations noted were:

1. Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation, including:
   - No source documentation by the physician or a designee for the physical examination and vital signs for Subjects 30-021 and 30-025.
   - No source documentation of the physician or designee reviewing procedures, completing drug accountability, or diary review on Days 4, 8, and 15 for all subject files reviewed.
   - No source documentation of the study phone calls performed on Days 2, 6, 12, and 14 for all subject files reviewed.
2. An investigation was not conducted in accordance with the investigational plan including:
   - An SAE was not reported to the IRB within the protocol specified time for Subject 30-005.
   - There was no documentation in the source records reviewed of conservative therapies tried prior to enrollment.
   - Study visits required for compassionate use (every 4 weeks until the drug had been discontinued for 30 days) were not performed according to the protocol.

Per the CIS, a confirmed natural disaster made the inspection extremely difficult. However, "The Audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data." With the exception of issues noted above, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication."

Medical Officer's Comments:

This reviewer appreciates the difficulty created by the natural disaster which destroyed records for Site # 30 (10 of 13 boxes) and Site # 31 (apparently all boxes were destroyed). The above noted observations for Site # 30 do not raise safety or efficacy concerns for this reviewer, however.

No addendum to the Establishment Inspection Report (EIR) was received as of the date of this review for Sites # 30 and # 31.

3.2 Compliance with Good Clinical Practices

The single 15-day Phase 3 study (Study Dic-301) appears to have been conducted in accordance the ethical principles originating from the Declaration of Helsinki and undertaken in accordance with the principles of Good Clinical Practice (GCP) as set

forth in the International Conference on Harmonization Guidelines for GCP (ICH-E6). Written informed consent, approved by the Institutional review Board (IRB)/Independent Ethics Committee (IEC), was obtained for all subjects.

The Debarment Certification dated June 8, 2012, available in the application states, "Duchesnay Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." "Within the previous 5 years, there have been no convictions, as described in sections 306(a) and (b) of the Federal Food, Drug, and Cosmetic Act, of the applicant and/or affiliated persons responsible for the development or submission of this application."

A waiver of pediatric studies for girls under 12 years of age and a deferral of pediatric studies for girls 12 through (b) (4) years of age was requested by Duchesnay at the Pre-NDA meeting of December 14, 2009 with DRUP. Per the final meeting minutes dated January 13, 2010, DRUP agreed that a waiver of pediatric studies for girls under age 12 and a deferral of pediatric studies for girls 12 through (b) (4) years of age was appropriate. DRUP will represent this position when it meets with the Pediatric Review Committee (PeRC) on Diclegis:

> "Diclectin® is intended to treat nausea and vomiting of pregnancy. As pre-adolescent girls do not become pregnant, Duchesnay Inc. is requesting a waiver from pediatric development in children under 12 years of age. Duchesnay Inc. plans to conduct a study in post-adolescent girls between the ages of 12 and (b) (4) after the NDA is approved and therefore is requesting a deferral for pediatric development in this age group. We will submit the pediatric development plan with our NDA. Does the Division agree that a pediatric waiver in children under 12 years of age and a deferral for children between the ages of 12 and (b) (4) is appropriate?"

Duchesnay, Inc. submitted a Proposed Pediatric Study Request, under IND 72300/S-029 on April 13, 2012. The (b) (4) study proposed to assess the (b) (4) 10 mg doxylamine plus 10 mg of pyridoxine tablets (b) (4) in a (b) (4) (b) (4) adolescent population 12 to (b) (4) years of age. Per the protocol, the rational for selecting this age group was three fold:

1. Pregnancy can occur in adolescents who have experienced menarche.
2. Dosing of adolescent teens is not expected to be qualitatively or quantitatively different from adult dosing. Per the submission, the critical age difference in quantity and quality of NVP has been shown to occur at 30 years of age.
3. Adolescents 12 to (b) (4) years of age consist of an older pediatric population, and are a less vulnerable population of pediatric studies when compared to young children or infants.

The primary objective of this Phase 1 PK and safety study was to:

(b) (4)

DRUP requested consults from the Pediatric and Maternal Health Staff (PMHS) and the Office of Pediatric Therapeutics (OPT) regarding the proposed (b) (4) study submitted on April 13, 2012. Consultation responses were received on December 3, 2012 and December 12, 2012, respectively. Duchesnay was advised, in a regulatory letter dated February 27, 2013:

1. (b) (4)

(b) (4)

c. The "safety component" of your proposed (b) (4) study (b) (4)

[redacted] (b) (4)

2. The available data are insufficient to support extrapolation of the findings from adults to adolescents. Therefore, your submission should included an adequately powered, safety and efficacy study in a pregnant adolescent population, 12- (b) (4) years of age, with a therapeutic need. Sparse PK sampling may be incorporated into the design of this study.

A revised, certified pediatric waiver request and a referenced publication was submitted to the NDA on December 18, 2012 in response to a DRUP request for information conveyed on November 14, 2012. The following information is presented:

Question 1. Identify pediatric age group(s) included in your waiver request.

- 0 month to 1 month
- 1 month to 2 years
- 2 years to 12 years

Duchesnay's Response:

"Note: A deferral of studies in children aged 12- (b) (4) years has been agreed with the FDA as recorded in the Pre-NDA Meeting Minutes Dated January 13, 2010. A Proposed Pediatric Study Request (PPSR) was filed to IND 72,300 in Serial 0029 on April 13, 2012."

"For the drug product Diclectin®, studies in the identified pediatric age groups are impossible or highly impractical because the number of pediatric patients is too small and geographically dispersed."

Medical Officer's Comments:

This reviewer concurs with the consultation responses provided by the Pediatric and Maternal Health Staff (dated December 3, 2012) and the Office of Pediatric Therapeutics (dated December 12, 2012) regarding the proposed [redacted] (b) (4) *study submitted on April 13, 2012.*

3.3 Financial Disclosures

The Applicant certified on FDA Form 3454 (10/09), dated June 8, 2012, that they "have not entered into any financial arrangement with the listed clinical investigators" "whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a)." The Applicant also certified "that each listed clinical investigator required to disclose to the sponsor whether the investigator had a

proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interest." The Applicant further certified "that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)." The 4 Phase 1 principle investigators in Canada and the 4 Phase 3 principle investigators in the U.S. are included.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Diclegis delayed release tablet contains 10 mg of doxylamine and 10 mg of pyridoxine. The two drug substances are both USP.

Each round, white, film-coated, delayed release tablet is imprinted with the pink image of a pregnant woman. Each delayed release tablets is composed of (b) (4)

Doxylamine is very soluble in water and alcohol, freely soluble in chloroform, and very slightly soluble in benzene and ether.

Pyridoxine is one of the compounds along with pyridoxal and pyridoxamine that can be called vitamin B_6. Pyridoxine differs from pyridoxamine by the methanol substituent at the 4-position versus the methylamine constituent of pyridoxamine. It is often used as the hydrochloride salt. Pyridoxine hydrochloride is used in oral supplements and injectable vitamins used to correct vitamin B_6 deficiency. Pyridoxine is freely water-soluble, slightly soluble in alcohol and acetone, and insoluble in ether.

(b) (4)

(b) (4)

(b) (4)

On November 27, 2012, Chemistry, Manufacturing and Controls (CMC) requested, but not limited to, the following information from the Applicant:

- Provide an identity test for the pyridoxine HCL drug substance.
- Submit a list of specific drug substance impurities for pyridoxine HCL, if any.
- Provide a listing of the drug product components or a letter of authorization to the appropriate DMF if there is one.
- State specifically what constitutes a positive identity test.
- Comment on the observation that significant numbers of cracked tablets were found during stability studies at 24-36 months (batches 1119, 1120, 1121) but not at 48 months. Cracks in the film coating have the potential to affect the dissolution properties of the drug product.

On January 7, 2013, CMC sent additional questions and comments to the Applicant:

- We remind you that you will need to submit an updated specification table and analytical method.
- We note that your stability data tables contain a line for the number of cracked tablets. Do you intend to propose a limit for the number of defective tablets or is this item included for informational purposes only?
- You have proposed a (b) (4) expiration date based on stability data from supportive batches. We note that cracked tablets were observed in those batches during stability testing beginning at 18 months. In light of only 3 months of stability data on the proposed commercial product and the observed cracks in the film coat of the supportive batches appearing at 18 months, we recommend an 18 month expiration dating period and note that it may be extended by annual report as described in 21 CFR 314.70 (d) (2) (vi).

Additional CMC information was requested on February 14, 2013:

- "A revised drug product specification sheet reflecting addition of a second identity test, analytical method of identity with validation report, and a revised expiry date proposal (24 months)."
- Based on the mean *in vitro* dissolution profiles from the clinical and primary stability batches at release and under long term stability, the following dissolution acceptance criterion for the buffer stage is recommended: Q = (b) (4) at 15 minutes. We recommend that you revise the dissolution acceptance criterion accordingly and submit an updated sheet of specifications for the drug product."

Medical Officer's Comments:

See the CMC Review for a discussion of the information provided by the Applicant in response to the requested CMC information. See also the CMC Review for the Agency's response to the information provided, and for final CMC recommendations regarding NDA 21876.

4.2 Clinical Microbiology

The application provides the following information regarding the monitoring of Diclegis delayed release tablets for microbial tests during routine release testing and on an annual basis during stability testing:

- Total plate count: ≤ 100 CFU/g
- Yeasts and molds: ≤ 10 CFU/g
- *Escherichia coli*: absence
- *Salmonella sp*: absence
- *Staphylococcus aureus*: absence
- *Pseudomonas aeruginosa*: absence

Medical Officer's Comments:

See the CMC Review for the final recommendations regarding Clinical Microbiology for NDA 21876.

4.3 Preclinical Pharmacology/Toxicology

Per the application, "The nonclinical evidence supporting the combination of doxylamine succinate and pyridoxine hydrochloride safety in Diclectin [sic] for this application, is based on the Agency's determination of the safety of the Reference Listed Drug (RLD), Bendectin® (NDA 10-598) according to section 505(b)(2) of the Federal Food Drug and Cosmetic Act." To further support the application, the Applicant performed a search of

the literature for publications that relate to the safety of doxylamine and pyridoxine individually and in combination. Selected reports are summarized in the application.

See the Pharmacology/Toxicology Review of NDA 21876 for a discussion of the published pharmacology/toxicology literature included in the application. Based on the Pharmacology/Toxicology Review, the reviewer recommends that the following information appear in Diclegis labeling under Subsection 8.1 Pregnancy, Animal Data:

"The effects of doxylamine succinate and pyridoxine hydrochloride in combination on embryofetal development have been studied in rats and monkeys. Once daily treatment of pregnant rats with doxylamine succinate and pyridoxine hydrochloride during organogenesis resulted in reduced maternal body weight and food consumption, reduced fetal body weight, and reduced fetal ossification in anterior distal limbs at doses 60 and 100 times the highest clinical dose (80 mg) based on body surface area. Increased fetal resorptions and skeletal variations (shortened 13^{th} rib) were observed at a dose 100 times the highest clinical dose (80 mg) based on body surface area.

Pregnant cynomolgus monkeys were treated once daily with doxylamine succinate and pyridoxine hydrochloride in combination during organogenesis (GD 22-50). At birth, there were no observed malformations, and no evidence of embryo, fetal or maternal toxicity at doses up to 3.2 times the highest proposed clinical dose (80 mg). In a separate study, pregnant cynomolgus and rhesus monkeys, and baboons were treated once daily with doxylamine succinate and pyridoxine hydrochloride in combination during organogenesis (GD 22-50), and their neonates were delivered and examined at GD 100. Ventricular septal defects (VSD) were observed in 6 (40%) of the preterm cynomolgus monkeys, 2 (18%) of the preterm rhesus monkeys and 3 (23%) of the preterm baboons examined prenatally (GD100) at doses 5-20 times (cynomolgus and rhesus monkeys) the highest proposed clinical dose (80 mg), and at doses 0.5-5 times (baboons) the highest proposed clinical dose (80 mg). No dose response was evident and there were no other cardiac or extracardiac defects found. No defects were observed in cynomolgus monkeys administered the combination of doxylamine succinate and pyridoxine hydrochloride for 4-day periods between 22 and 41 days of gestation. There was no incidence of VSD in infant monkeys examined at term, though one cynomolgous monkey had a mitral valve defect".

Bendectin® (10 mg Doxylamine Succinate/10 mg Pyridoxine Hydrochloride) Delayed Release Tablets Labeling:

The following preclinical information appears in the Bendectin® Labeling, provided in the application, obtained from the 1982 Physician's Desk Reference:

"Teratology studies with Bendectin or its two components (doxylamine succinate and pyridoxine hydrochloride) have been reported in various animal species, including:

Sprague-Dawley and Wister rats, New Zealand and Dutch-belted rabbits, NMRI mice, rhesus (*M. mulatta)* and cynomolgus (*M. fascicularis*) monkeys. The majority of studies did not demonstrate a teratogenic effect on Bendectin or its components. However, two of the most recent studies, although preliminary and unconfirmed, raise the possibility that Bendectin or doxylamine succinate may have a teratogenic potential in some species, as indicated below. Studies of Bendectin in Sprague-Dawley rats and New Zealand rabbits at doses up to 90 times the maximum human dose (MHD) gave no indication of drug-induced fetal abnormalities."

"A small study in pregnant cynomolgus monkeys treated throughout organogenesis with Bendectin (10-20 times the MHD) indicated defects in the interventricular septum of the heart in 4 of 7 fetuses that were delivered on day 100 of gestation (total gestation time approximately 160 days). Two fetuses from aborted pregnancies on day 46 and 56 appeared to be developing normally. Three additional fetuses allowed to go to term were normal. In other experiments, pregnant rhesus and cynomolgus monkeys treated with Bendectin for shorter periods of time delivered normal fetuses."

"Studies of doxylamine succinate at doses up to 60 times the MHD in Wistar rats and NMRI mice, and up to 125 times the MHD in Sprague-Dawley rats and Dutch-belted rabbits gave no indication of observable congenital abnormalities. At doses of 125 to 375 times the MHD in Wistar rats, wavy-ribs (7-10%) and diaphragmatic hernias (2-6%) were noted. An overall increase in fetal wastage which varied from zero to 30 fold was reported for a majority of rodent species given doses of 125 times the MHD or more."

Per additional literature information provided in the application, pregnant primates were given ten (10) times the maximum human daily dose of doxylamine/pyridoxine from day 22 to 50 of pregnancy. "The study results indicated that the pharmacokinetics of Doxylamine did not significantly differ throughout pregnancy despite the major changes in volume of distribution, protein binding and clearance rate seen in later pregnancy. These findings suggest that pharmacokinetic studies in nonpregnant women are likely to accurately reflect Doxylamine PK characteristics during the first trimester of pregnancy when NVP is most prominent."[7]

Medical Officer's Comments:

The Pharmacology/Toxicology reviewer recommends that the following information appear in Diclegis labeling under Subsection 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility, and a proposed Subsection 13.2 Animal Toxicology and/or Pharmacology, respectively:

"13.1 Carcinogenesis, Mutagenesis and impairment of Fertility

7 Rowland JM et al. Pharmacokinetics of doxylamine given as Bendectin in the pregnant monkey and baboon. Reprod Toxicology. 1989;3:197-202.

Carcinogenicity

Two-year carcinogenicity studies in rats and mice have been conducted with doxylamine succinate. The results were of questionable significance in humans, and doxylamine succinate is not likely to have human carcinogenic potential."

"13.2 Animal Toxicology and/or Pharmacology

The effects of doxylamine succinate and pyridoxine hydrochloride in combination on embryofetal development have been studied in rats and monkeys. Once daily treatment of pregnant rats with doxylamine succinate and pyridoxine hydrochloride during organogenesis resulted in reduced maternal body weight and food consumption, reduced fetal body weight, and reduced fetal ossification in anterior distal limbs at doses 60 and 100 times the highest clinical dose (80 mg) based on body surface area. Increased fetal resorptions and skeletal variations (shortened 13th rib) were observed at a dose 100 times the highest clinical dose (80 mg) based on body surface area.

Pregnant cynomolgus monkeys were treated once daily with doxylamine succinate and pyridoxine hydrochloride in combination during organogenesis (GD 22-50). At birth, there were no observed malformations, and no evidence of embryo, fetal or maternal toxicity at doses up to 3.2 times the highest proposed clinical dose (80 mg). In a separate study, pregnant cynomolgus and rhesus monkeys, and baboons were treated once daily with doxylamine succinate and pyridoxine hydrochloride in combination during organogenesis (GD 22-50), and their neonates were delivered and examined at GD 100. Ventricular septal defects (VSD) were observed in 6 (40%) of the preterm cynomolgus monkeys, 2 (18%) of the preterm rhesus monkeys and 3 (23%) of the preterm baboons examined prenatally (GD 100) at doses 5-20 times (cynomolgus and rhesus monkeys) the highest proposed clinical dose (80 mg), and at doses 0.5-5 times (baboons) the highest proposed clinical dose (80 mg). No dose response was evident and there were no other cardiac or extracardiac defects found. No defects were observed in cynomolgus monkeys administered the combination of doxylamine succinate and pyridoxine hydrochloride for 4-day periods between 22 and 41 days of gestation. There was no incidence of VSD in infant monkeys examined at term, though one cynomolgous monkey had a mitral valve defect.

See the Pharmacology/Toxicology Review for final recommendation regarding NDA 21876.

4.4 Clinical Pharmacology

Per the application, because doxylamine was approved before strict investigative protocols were required by regulatory agencies, very few studies have examined the pharmacokinetics of this compound in female patients.

(b) (4)

Study 02163 (relative bioavailability study under fasting condition) and Study 02191 (relative bioavailability study under fed conditions). However, an independent audit of these studies cast doubt on the dependability of these studies (see Subsection 3.1 Submission Quality and Integrity of this review). Based on these audit findings, Duchesnay conduct a new food effect study (Study 70294) and a new pharmacokinetic study (Study 70381). The results of Studies 70294 and 70381 are presented in the application. The results of Studies 02163 and 02191are also presented in the application, but these two studies are considered supportive of Diclegis safety only.

4.4.1 Mechanism of Action

Per the application, doxylamine is biotransformed in the liver by n-dealkylation to its principle metabolites, N-desmethyldoxylamine and N, N-didesmethyldoxylamine, which are excreted by the kidneys

Pyridoxine is a prodrug that undergoes complex metabolic transformation in the blood resulting in the metabolites: pyridoxal, pyridoxal 5'-phosphate, pyridoxamine and pyridoxamine 5'-phosphate. Pyridoxine is readily absorbed in the gastrointestinal tract, mainly in the jejunum and is primarily metabolized in the liver. The pharmacokinetics and disposition of vitamin B_6 are very complex and some metabolites have biological activity.

Per the application, vitamin B_6 in coenzyme form performs a wide variety of functions in the body with involvement in more than 100 enzyme reactions. These are mostly concerned with protein metabolism, amino acid metabolism and metabolism of one-carbon units, carbohydrates, and lipids. Vitamin B_6 plays a role in cognitive development through the biosynthesis of neurotransmitters and in maintaining normal levels of homocysteine, an amino acid in the blood. Vitamin B_6 is also involved in gluconeogenesis and glycogenolysis, immune function (it promotes lymphocyte and interleukin-2 production), and hemoglobin formation.

4.4.2 Pharmacodynamics

Numerous literature references are provided in the application for doxylamine (13 references) and pyridoxine (11 references).

Per the application, "Limited pharmacokinetic data are available for doxylamine and other older, first generation antihistamines. Because doxylamine is primarily metabolized by the liver, and both parent drug and metabolites are excreted in the urine, patients with renal and/or liver disease may be at greater risk for adverse effects due to drug and metabolite accumulation. Therapy with doxylamine should be administered cautiously in such patients."

Per the application, "About half of the intake of vitamin B_6 is excreted as the inactive 4-pyridoxic acid in urine. Vitamin B_6 is also excreted in feces but to a limited extent."

Medical Officer's Comments:

See the Clinical Pharmacology Review of NDA 21876 for a full discussion of the submitted literature.

4.4.3 Pharmacokinetics

As previously noted in this review, two new Phase 1 bioavailability studies were completed (Study 70294 and Study 70381) to replace 2 previously completed Phase 1 bioavailability studies (Study 02163 and Study 02191) when the data from the earlier studies were considered unreliable.

Phase 1 Study 70294:

Study 70294 entitled, "Randomized, Open-Label, 2-Way, Crossover, Relative Bioavailability Study of Doxylamine-Pyridoxine 10 mg-10 mg (Diclectin) Delayed-Release Tablets Following a 2 x 10 mg-10 mg Dose in Healthy Adult Females under Fasting and Fed Conditions" was a single center, comparative bioavailability, open-label, single-dose, randomized, 2-way crossover study in which 44 women were confined to the (b) (4) at least 10 hours prior to drug administration and until after the 24 hour post dose blood draw in each period. All subjects were fasted at least 10 hours prior to drug administration and those in the fed group received a standard high-fat, high-caloric meal 30 minutes before drug administration. All subjects were subsequently fasted for a period of at least 4 hours. The treatment period (fed and fasted) were separated by a period of 27 days. Of the 44 women enrolled in Study 70294, 42 subjects completed the study.

Per the application, the administration of Diclegis with a standard high-fat, high-caloric meal delayed the absorption of both doxylamine and pyridoxine by approximately 7 hours when compared to administration under fasting conditions based on median t_{max} results. The T_{max} ± SD values under fasted/fed conditions were 5.13 ± 3.39/14.9 ± 7.4 for doxylamine and 2.50 ± 0.94/9.25 ± 3.96 for pyridoxine. "This delay in absorption under fed conditions was associated with a lower peak concentration of doxylamine, but the extent of absorption was not affected." "The rate and extent of absorption of

pyridoxine was significantly reduced when administered with food; however, the effect of food on the pyridoxine component is more complex because of the active metabolites." Based on the results in Study 70294, the Applicant concludes that food decreases the rate of absorption of Diclegis but does not affect the overall extent of absorption.

Medical Officer's Comments:

In information provided by the Clinical Pharmacology reviewer for NDA 21876, the reviewer concurs with the Applicant that food delayed the C_{max} of both doxylamine and pyridoxine by approximately 7 hours (based on median T_{max} results). The C_{max} of doxylamine and pyridoxine and pyridoxine metabolites are also reduced with food. The half-life of doxylamine is approximately 12 hours. However, the half-life of pyridoxine is very short (< 30 minutes).

Per the Clinical Pharmacology information provided, the following main conclusion can be made for Study 70294:

- *"When taken with food, a delay in T_{max} was observed, as well as a reduction in both C_{max} and AUC of the parent drugs and pyridoxine metabolites."*
- *"---, there was high variability in the data primarily associated with undetectable plasma levels in many subjects during the terminal elimination phase. For example, %CV for one of the pyridoxine metabolites, pyridoxamine, was 337.16% (Table 1.3.3)."*

See the Clinical Pharmacology Review to view Table 1.3.3, and for a full discussion of the reported findings in Study 70294.

Phase 1 Study 70381:

Study 70381 entitled "Single and Multiple Dose Safety and Pharmacokinetic Study of Diclectin® in Healthy Non-pregnant Female Subjects" is a single center, single and multiple dose, open-label study in which 18 women were confined to the (b) (4) at least 28 hours prior to first drug administration and were discharged from the clinic on Day 20, after the 36 hour post-last dose blood draw. Subjects presented themselves for all subsequent blood draws on Days 21 and 23. Subjects were administered a single dose of Diclegis (2 delayed-release tablets) at 22:00 hours on Days 1 and 2, and were administered multiple oral doses from Days 3 through 18 as follows: 1 delayed-release tablet at 09:00 and 16:00 hours, and 2 delayed-release tablets at 22:00 hours under empty-stomach conditions (defined as at least 2 hours after eating). All 18 subjects completed Study 70381.

Study 70381 assessed the following parameters:

- Single dose pharmacokinetic (PK) parameters (Days 1 and 2): $Auc_{0\text{-last}}$, $Auc_{0\text{-}24}$, $AUC_{0\text{-inf}}$, C_{max}, T_{max}, K_{el} and $T_{1/2el}$.
- Multiple dose PK parameters (Days 18-23): $Auc_{0\text{-last}}$, $Auc_{0\text{-}24}$, $AUC_{0\text{-inf}}$, C_{max}, $C_{min0\text{-}24}$, C_{ave}, T_{max}, K_{el} and $T_{1/2el}$, AI, CL and V_{dss}.

No value for K_{el}, $AUC_{0\text{-inf}}$, or $T_{1/2el}$ was reported for cases that did not exhibit a terminal log-linear phase in the concentration-time profile.

Per the application, the doxylamine results indicate the following:

- Multiple dose administrations of Diclegis (compared to single dose administration) increased C_{max} from 83.26 ± 20.62 ng/mL to 168.58 ± 38.49 ng/mL and extent of absorption ($Auc_{0\text{-}24}$) from 911.40 ± 205.62 ng.h/mL to 2531.40 ± 719.47 ng.h/mL.
- Multiple doses did not affect the time to reach maximum concentration
- Steady state for doxylamine was attained after Day 9 based on pre-dose concentration observed on Days 9 thru18 and Day 18.

Human doxylamine plasma level concentration data (AUC), from combining literature results and Duchesnay's relative bioavailability data for Study 70294 and Study 70381 demonstrate "non-linear pharmacokinetics over the dose range of 10 to 40 mg".

Per the application, the pyridoxine and pyridoxine metabolites results "have to be interpreted with caution due to low concentrations detected and the high variability." The pyridoxine and pyridoxine metabolites results indicate the following:

- Single or multiple dose administration did not significantly affect the concentration of pyridoxine and the metabolite pyridoxamine.
- Multiple dose administration increased the concentrations of the metabolites pyridoxal, pyridoxal 5'-phosphate, and pyridoxamine 5'-phosphate.
- Multiple dose administration increased the extent of absorption ($Auc_{0\text{-}24}$) of pyridoxine and pyridoxine metabolites pyridoxal, pyridoxamine, and pyridoxamine 5'-phosphate.
- Multiple dose administration did not seem to affect the time to reach the maximum concentration (T_{max}).
- Steady state was reached within 9 to 11 days for pyridoxine and pyridoxine metabolites pyridoxal, and pyridoxal 5'-phosphate.
- The accumulation index of pyridoxine suggests accumulation after multiple doses (~1.5 fold). Per the application, pre-dose concentrations on Days 9 to 17 and Day 18 suggest that pyridoxine does not accumulate after multiple dose administration.

Medical Officer's Comments:

In information provided by the Clinical Pharmacology reviewer for NDA 21876, the following comments regarding Study 70381 are provided:

- *The exposure of doxylamine (C_{max} and AUC) significantly increased following multiple doses compared to a single dose. The mean accumulation index (ratio of AUC_{0-24} Day 18/AUC_{0-24} Day 1) was more than unity (2.76) suggesting that doxylamine accumulates following multiple doses.*
- *Steady state of doxylamine appears to be achieved after Day 9.*
- *Overall, the concentration of pyridoxine was higher after multiple dose administration than after a single dose. The accumulation index reflects approximately 1.6 fold increases after multiple dose administration compared to a single dose.*

Per the information provided by the Clinical Pharmacology reviewer, the following main conclusion can be made for Study 70381:

- *"The parent drugs and metabolites accumulate in the body following multiple dose administration for C_{max} and AUC of doxylamine (Figures 1.3.1-1.3.3 and Tables 1.3.1 and 1.3.2) and pyridoxine (Figures 1.3.4 and 1.3.6 and Tables 1.3.1 and 1/3/2).*
- *The half-life generally increased for all components of the product (Table 1.3.2).*
- *There was high variability in the data which is primarily associated with low and undetectable concentration in the terminal elimination phases. For these reasons the elimination rate constants were not adequately determined or mostly could not be determined in many subjects. Therefore, the determinations of the half-life and the AUC to infinity were not adequate in many situations and should be interpreted carefully."*

See the Clinical Pharmacology Review to view the Figures and Tables mentioned above. See the Clinical Pharmacology Review for final recommendations regarding NDA 21876.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

(b) (4)

Study 02163 (relative bioavailability study under fasting condition) and Study 02191 (relative bioavailability study under fed

conditions). However, an independent audit of these studies cast doubt on the dependability of these studies (see Subsection 3.1 Submission Quality and Integrity of this review). Studies 02163 and 02191 are considered supportive of Diclegis safety only.

Table 2: Diclegis Clinical Studies and Relevant Formulations

Clinical Study	Study Type	Drug Product Batch	Notes:
Study 70294	Food effect	Lot No, 1120	Commercial formulation
Study 70381	Pharmacokinetics	Lot No. 1120	Commercial formulation
Study DIC-301	Safety and efficacy	Lot No. 1120	Commercial formulation

Source: Adapted from NDA 21876, Clinical Overview, Table 2.5-3, page 14 of 61.

5.2 Review Strategy

The available clinical data for 15-day Phase 3 Study DIC-301 and the available clinical data in NDA 10598 for Bendectin provide the basis for consideration regarding the safety and efficacy of Diclegis for the treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management.

5.3 Discussion of Individual Studies/Clinical Trials

Study DIC-301 entitled, "A Double-Blind, Multicenter, Randomized, Placebo-Controlled Trial of the Efficacy of Diclectin® for Nausea and Vomiting of Pregnancy" was a double-blind, randomized, multicenter (6 centers), placebo-controlled, parallel group study of Diclegis (10 mg doxylamine succinate plus 10 mg pyridoxine hydrochloride) for the treatment of pregnant women at least 18 years old with nausea and vomiting of pregnancy (NVP) and a Pregnancy Unique Quantification of Emesis (PUQE) score $\geq$ 6. The minimum assigned study medication was 2 tablets daily, at bedtime, increasing when indicated (PUQE score ≥ 3) to a maximum dosage of 4 tablets per day (refer to the following paragraph for dosage adjustment regimen). The first subjects began Study DIC-301 on February 7, 2008. The last subject completed Study DIC-301 on June 16, 2009.

Two tablets of Diclegis were administered at bedtime on Day 1. If symptoms of nausea and vomiting persisted into the afternoon hours of Day 2, the subject was directed to take her usual dose of 2 tablets at bedtime and an additional tablet the next morning on Day 3. Based upon assessment in the clinic on Day 4 (± 1 day), the subject may have been directed to take an additional tablet mid-afternoon to control evening symptoms.

As the primary objective of this protocol was to control symptoms of NVP, the number of tablets given to the subject depended on her PUQE score. If two evening tablets did not eradicate her symptoms (i.e., PUQE score was still above 3), she received a third

tablet the next morning. If with 3 tablets her PUQE score was still above 3, a 4th tablet was added in the mid-afternoon. While all subjects received 2 tablets before sleep, the dosage schedule was individualized according to the timing, duration, severity, and frequency of the symptoms experienced by the subject. The maximum number of tablets taken daily was 4, however.

Medical Officer's Comments:

The dose titration scheme followed in Study DIC-301 is the same dosage regimen recommended in labeling approved for Bendectin®, "2 Bendectin tablets at bedtime. In severe cases or when nausea occurs during the day: 1 additional Bendectin tablet in the morning and another in midafternoon."

The secondary efficacy endpoints included evaluation of the three individual components constituting the PUQE score (vomiting, nausea, and retching), the Global Assessment of Well Being, the number of tablets taken, the time loss from household tasks and/or employment, the total number of visits and phone calls to health care providers, the rates of hyperemesis gravidarum, and, finally, the compliance with study medication regimen.

Each delayed release tablets contained 10 mg doxylamine/10 mg pyridoxine (manufacturer batch/lot number: #1120). The placebo tablets were identical in size, shape, taste, and color (manufacturer batch/lot number: #1122).

Study DIC-301 had a 15 day period consisting of 14 dosing days. Subjects returned to the clinic prior to their morning dose on Day 4 (± 1 day), Day 8 (± 1 day), and on Day 15 (± 1 day; end of study visit) in order to time the drawing of blood samples to correspond with steady state trough levels (12 mL sample was collected for PK measurements of pyridoxine, pyridoxal, pyridoxal 5-phosphate, and doxylamine concentrations). Additionally, telephone contact was made at Day 2, 6, 12, and 14 in order to assess subject diary information, adverse events (AEs), concomitant medication use, and compliance with the study medication. Laboratory tests were conducted on Day 1 and Day 15.

Subjects were instructed on how to use the PUQE tool and completed the PUQE score (once daily every morning prior to the administration of the study dose at approximately the same time each day) and the study diary. The Day 15 PUQE score reflected the subject's response to treatment on Day 14. Subjects completed the Global Assessment of Well-Being on Days 1, 8, and 14 at the same time that the PUQE score was completed. Subjects were instructed to indicate their general state of well-being over the last week compared to their pre-pregnancy state of health.

A 12 mL blood sample was collected for pharmacokinetic measurements of pyridoxine, pyridoxal, pyridoxal 5'-phosphate and doxylamine concentrations on Day 1, Day 4 (± 1

day), Day 8 (± 1 day), and Day 15 (± 1 day) as recommended by DRUP.

Adverse events (AEs) and use of concomitant medications were recorded at all visits and phone calls. The frequency and severity of all AEs were collected from subject diaries and visit and phone call interviews and tabulated by treatment group, system organ class (SOC), preferred term, severity, and relationship to study medication. The AE relationship to plasma/whole blood drug concentrations (collected on Days 1, 4, 8, and 15) was also evaluated. In addition, laboratory tests were conducted on Day 1 and Day 15 (± 1 day). An obstetric ultrasound and physical examination including vital signs were conducted on Day 1.

If compassionate use of medication was warranted after Day 15, drug accountability and dispensing was conducted at clinic visits and AEs were reported during the Diclegis compassionate use period. All adverse events that were reported during the first 30 days of compassionate use treatment were recorded on the case report form (CRF). After the first 30 days of compassionate use treatment, only serious adverse events (SAE) were reported.

Inclusion Criteria:

Subjects were eligible for study inclusion if they met all of the following inclusion criteria:

1. Had signed a written informed consent to participate in the study and agreed to follow dosing instructions and complete all required study visits.
2. A pregnant female age equal to or greater than 18 years old.
3. Had an entry ultrasound indicated a viable pregnancy and the confirmed gestational age of the fetus was 7-14 weeks at the anticipated time of the first dose of study medication or placebo. If an ultrasound was done within 4 weeks of the admission visit, and results could be obtained, an additional ultrasound was not necessary.
4. Was suffering from NVP and had a PUQE score ≥ 6.
5. Had not responded to conservative management consisting of dietary/lifestyle advice according to the 2004 ACOG Practice Bulletin.
6. Agreed, if on a multivitamin, to continue on their current dose of multivitamin for the duration of the trial.
7. Did not plan termination of the pregnancy.

Exclusion Criteria:

Subjects were excluded from study participation if they met any of the following exclusion criteria:

1. Investigator confirmed the subject's nausea and vomiting was of etiology other than NVP.
2. Had gestational trophoblastic disease or multifetal gestation.

3. Had a condition for which antihistamines, in the opinion of the investigator, were contraindicated (epilepsy, alcoholism, glaucoma, chronic lung disease, urinary retention, heart block, etc.).
4. Had used antihistamines, anticholinergics, dopamine antagonists, serotonin antagonists, ginger, or anti-emetic therapy (including acupressure, acupuncture, homeopathic remedies, medical hypnosis, relief bands, etc) to treat NVP in the previous 48 hours or planned to do so during the study.
5. Was using drugs that had anticholinergic activity (e.g., tricyclic antidepressants).
6. Was taking multivitamins containing more than 10 mg of vitamin B6, or planned to do so during the study.
7. Was taking supplementary vitamin B_6 in addition to any multivitamin preparation, or planned to do so during the study.
8. Was currently drinking any amount of alcohol.
9. Had any condition that might have interfered with the conduct of the study.
10. Was likely to be unable to comply with study procedures because of inadequate cognitive skills.
11. Had received an investigational drug within 30 days before enrollment in this study or was scheduled to receive an investigational drug during the course of this study

Medical Officer's Comments:

The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin, Nausea and Vomiting of Pregnancy, Number 52, April 2004 provides guidelines to obstetrician-gynecologists on the clinical management of nausea and vomiting of pregnancy.

Per the ACOG Practice Bulletin, common nonpharmacologic therapies recommended to alleviate initial signs of nausea and vomiting of pregnancy include:

- *rest and avoidance of sensory stimuli that provoke symptoms,*
- *frequent, small meals,*
- *avoid spicy or fatty foods,*
- *eliminate pills with iron,*
- *eat bland or dry foods,*
- *eat protein snacks, and*
- *eat crackers in the morning before arising.*

In addition, the ACOG Practice Bulletin provides the following Summary of Recommendations as the best available evidence about the diagnosis and management of NVP:

"The following recommendations are based on good and consistent scientific evidence (Level A):

- *Taking a multivitamin at the time of conception may decrease the severity of nausea and vomiting of pregnancy.*
- *Treatment of nausea and vomiting of pregnancy with vitamin B_6 or B_6 plus doxylamine is safe and effective and should be considered first-line pharmacotherapy.*
- *In patients with hyperemesis gravidarum who also have suppressed thyroid-stimulating hormone levels, treatment of hyperthyroidism should not be under taken without evidence of intrinsic thyroid disease (including goiter and/or thyroid autoantibodies).*

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- *Treatment of nausea and vomiting of pregnancy with ginger has shown beneficial effects and can be considered as a nonpharmacologic option.*
- *In refractory cases of nausea and vomiting of pregnancy, the following medications have been shown to be safe and efficacious in pregnancy: antihistamine H_1 receptor blockers, phenothiazines, and benzamides.*
- *Early treatment of nausea and vomiting of pregnancy is recommended to prevent progression to hyperemesis gravidarum.*
- *Treatment of severe nausea and vomiting of pregnancy or hyperemesis gravidarum with methylprednisolone may be efficacious in refractory cases; however, the risk profile of methylprednisolone suggests it should be a treatment of last resort.*

The following recommendations are based primarily on consensus and expert opinion (Level C):

- *Intravenous hydration should be used for the patient who cannot tolerate oral liquids for a prolonged period or if clinical signs of dehydration are present. Correction of ketosis and vitamin deficiency should be strongly considered. Dextrose and vitamins, especially thiamine, should be included in the therapy when prolonged vomiting is present.*
- *Enteral or parental nutrition should be initiated for any patient who cannot maintain her weight because of vomiting."*

Hyperemesis gravidarum is defined as any visit to any healthcare provider, inpatient or outpatient, where intravenous fluids are administered for dehydration or electrolyte imbalance due to NVP.

Removal of Subjects from Study:

Per the application, the investigator could terminate a subject's study participation at any point during the trial. In addition, a subject could discontinue her participation at any time during the study. Subjects for whom treatment with the maximal dosage of 4

tablets per day did not provide adequate control of symptoms during the study period, as determined by the subject or study physician, were instructed to discontinue study drug and visit the study center. They were asked to return unused tablets, completed forms, and the daily diaries.

If any test results received after study start constituted a reason for excluding a subject, the subject was informed at once.

Should a subject's participation be discontinued, it was required that the reason(s) be recorded in the source documents and on the CRF. In addition, efforts were to be made to perform all Day 15 procedures for the Early Termination Visit. Discontinued or withdrawn subjects were not replaced. The primary reason for treatment discontinuation was noted in the CRF using the following categories:

- Adverse event
- Protocol deviation
- Withdrawal of consent
- Death
- Lost to follow-up
- subject unblinding
- Investigator discretion
- Treatment failure

Prohibited Medications:

If any other treatment was used, including non-pharmacological treatments, an accurate record was kept in the source documentation and the CRF. This record included the name of the treatment, the dose, the date(s) of administration, and the reason for use. Any comfort measure used to treat NVP was also documented in the diary.

The following medications were prohibited during the study: multivitamins containing more than 10 mg of vitamin B_6, supplementary vitamin B_6, antihistamines, other anti-emetic therapy including, but not limited to anticholinergics, dopamine antagonists, serotonin antagonists, ginger dietary supplement, acupressure, acupuncture, homeopathic remedies, medical hypnosis, relief bands (used to treat NVP) and drugs that have significant anticholinergic activity (for example, tricyclic antidepressants).

Treatment Compliance:

Bottles of study medication were supplied to each subject with the Day 1 visit. Study medication administration was discussed with the subject in order to ensure accuracy and compliance throughout the trial. Subjects self-administered daily oral doses of Diclegis or placebo for 14 days. The investigator or designee was responsible for taking

an inventory of the investigational agent. A record of this inventory documenting return of study drug and a drug dispensing log were maintained.

Assessment of Efficacy:

The primary efficacy assessment was the Pregnancy-Unique Quantification of Emesis (PUQE) score. The PUQE score measured:

- the severity of vomiting (number of vomiting episodes per day),
- the severity of nausea (number of hours of nausea per day), and
- the severity of retching (number of retching/heaving episodes per day)

for an overall score of symptoms rated from 3 (no symptoms) to 15 (most severe).

The subject completed the baseline PUQE in the clinic on Day 1. To qualify for study participation, the subject must have had a PUQE score ≥ 6. The subjects then completed the PUQE once daily every morning prior to study dose, at approximately the same time each day, to evaluate the previous 24 hours (Days 2 through study completion/early termination). See the following illustration.

Pregnancy Unique-Quantification of Emesis

Motherisk PUQE Scoring System (*please tick box and write total score)*

1. In the last 24 hours, for how long have you felt **nauseated or sick at your stomach**,	Not at all (1)	1 hour or less (2)	2-3 hours (3)	4-6 hours (4)	More than 6 hours (5)
2. In the last 24 hours, have you **vomited or thrown up**,	7 or more times (5)	5-6 (4)	3-4 (3)	1-2 (2)	I did not throw up (1)
3. In the last 24 hours, **how many** times have you had **retching or dry heaves** without bringing anything up,	No time (1)	1-2 (2)	3-4 (3)	5-6 (4)	7 or more (5)

Global Assessment

How many hours have you slept out of 24 hours?_____

If this is not your normal sleep hours, Why?_____

On a scale of 0-10, how would you rate your *Well Being* in the last week?____

Reference Scale 0 (Worst possible) to 10 (The best you felt before pregnancy)

Can you tell me what causes you to feel that way?

_____

_____

Per the Applicant, "The external validity of PUQE has been assessed by examining data collected prospectively from 315 women counseled by the Motherisk NVP line."

Medical Officer's Comments:

The Motherisk NVP Healthline is a helpline of The Motherisk Program at the Hospital for Sick children, Toronto, Canada. It is a helpline developed to provide counseling to pregnant women experiencing nausea and vomiting of pregnancy. Women who contact the helpline receive counseling on strategies such as lifestyle changes, and receive advice about medication to manage NVP symptoms. "The NVP counselors also collect data from women as part of evaluation and follow-up of those managed for NVP."

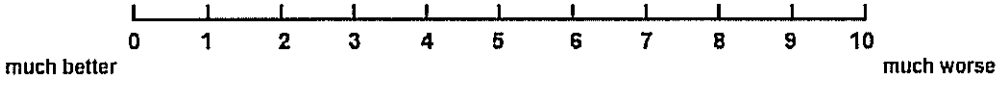
Secondary Efficacy Assessments:

The secondary efficacy assessments included the following:

- Three individual components constituting the PUQE score
- Global Assessment of Well-Being
- Number of tablets taken
- Time loss from household tasks and/or employment
- Total number of visits and phone calls to healthcare providers
- Rates of hyperemesis gravidarum
- Relationship between levels of vitamin B6 (total and metabolites) and doxylamine and PUQE score

The Global Assessment of Well-Being component was completed by the subject on Days 1, 8, and 14. The subject selected a number on a scale, as shown below, of 0 (worst possible) to 10 (best) to reflect her general state of well-being over the last week compared to her pre-pregnancy state of health. See the following illustration.

Please put a mark on this line to show how you have been feeling IN GENERAL (not just nausea and vomiting) over the last week compared to your usual state of health.



Daily Diary:

The subject used a daily diary to record:

- information about medication,
- symptoms other than NVP,
- visits and phone calls to healthcare providers,
- time lost from household tasks,
- time lost from employment,
- completion of the PUQE score, and the
- Global Assessment of Well-Being (Days 1, 8, and 14).

The diary was to be completed in the clinic on Day 1, once daily every morning prior to study dose, at approximately the same time each day to evaluate the previous 24 hours on Days 2 through Day 15.

Assessment of Safety:

Safety assessments included a medical history obtained on Day 1, a physical examination including vital signs (height, weight, temperature, heart rate, and blood pressure) performed on Day 1, an obstetric ultrasound performed on Day 1 to document viable pregnancy and gestational age as well as to exclude gestational trophoblastic disease and multifetal gestation.

A 10 mL clinical laboratory blood sample and urine sample were obtained on Day 1 and Day 15. The time of the last dose of study medication, as well as the time the laboratory test was taken, was recorded on the CRFs. All samples were collected in accordance with acceptable laboratory procedures. Subjects were instructed to fast prior to collection of blood specimens for laboratory analysis.

Table 3: Laboratory Parameters Assessed for Safety in Study DIC-301

Hematology	Serum Chemistry	Urinalysis
Hematocrit	Albumin	Appearance
Hemoglobin	Alkaline phosphatase	Color
Red blood cell count	Alanine transaminase	pH
Platelet count	Amylase	Specific gravity
White blood cell count (*with differential*)	Aspartate transaminase	Protein
Neutrophils	Blood urea nitrogen	Glucose
Monocytes	Calcium	Ketones
Eosinophils	Carbon dioxide	Nitrite
Basophils	Chloride	Bilirubin
	Creatinine	Urobilinogen
	Gamma glutamyl transferase	Hemoglobin
	Glucose	
	Lactate dehydrogenase	
	Magnesium	
	Phosphorus	
	Potassium	
	Sodium	
	Total and Direct bilirubin	
	Total cholesterol	
	Total protein	
	Triglycerides	
	Uric acid	

Medical Officer's Comments:

The safety assessments were standard, and generally recognized as reliable and relevant.

A 12 mL blood sample was collected for pharmacokinetic measurements of pyridoxine, pyridoxal, pyridoxal 5'-phosphate and doxylamine concentrations on Day 1, Day 4 (± 1 day), Day 8 (± 1 day), and Day 15 (± 1 day). Total vitamin B_6 concentration was calculated by adding the concentrations of pyridoxine, pyridoxal, and pyridoxal 5'-phosphate for each sampling time for every subject and by rounding off to 3 significant digits. The plasma levels of pyridoxine, pyridoxal, and pyridoxal 5'-phosphateand doxylamine were measured by liquid chromatography tandem mass spectrometry (LC/MS/MS) methods by the designated bioanalytical laboratory (b) (4)

The blood sample was drawn prior to the morning dose of study drug on Day 4 (± 1 day), Day 8 (± 1 day), and Day 15 (± 1 day) to represent steady state trough levels. All

laboratory samples had the time of the test recorded as well as the time of the last dose of study drug.

Adverse Events (AEs):

An AE was defined as any untoward medical occurrence, whether or not related to the study product, experienced by a subject. An AE may have consisted of a disease, an exacerbation of a pre-existing illness or condition, a recurrence of an intermittent illness or condition, a set of related signs or symptoms, a single sign or symptom, a clinically significant laboratory test result, or an abnormality discovered by physical examination. Any illness that worsened in severity after treatment initiation was considered an AE.

The severity of the AE was assessed according to the following guidelines:

Mild: not limiting usual activities
Moderate: some limitations of usual activities
Severe: causing inability to perform usual activities

The investigator made a determination of the relationship of the AE to the study drug using the following guidelines:

Not Related: An AE that did not follow a reasonable temporal sequence from administration of the drug and that could be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment.

Unlikely: An AE that followed a reasonable temporal sequence from administration of the drug, but there was not a reasonable causal relationship between the administration of the drug and the AE.

Possible: An AE that followed a reasonable temporal sequence from the administration of the drug (including the course after withdrawal of the drug) and that could not be excluded as being possibly caused by the drug (e.g., existence of similar reports attributed to the suspected drug and/or its analogues; reactions attributable to the pharmacological effect of the drug), although other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment were presumable.

Probable: An AE that followed a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug) and that could be excluded as being possibly caused by other factors, such as underlying disease, complications, concomitant drugs, or concurrent treatment.

Definite: An AE that followed a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug), or followed a known or hypothesized cause effect relationship.

All AEs collected were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 10.0 or higher), classified by system organ class (SOC) and preferred term (PT).

The investigator was responsible for recording and reporting AEs observed during the study. The report must have included date of onset, a description of the AE, severity, seriousness, action taken, relationship to the study medication, outcome of the event, and date of resolution. The investigator provided appropriate information concerning findings that suggested significant hazards or side effects that occurred during the study. Any complaints were noted as an AE and managed according to standard practice. Adverse events were to be collected through Day 15 or the Early Termination Visit. For subjects who continued to receive medication for compassionate use, AEs were collected for the 30 days following dispensation of the compassionate drug.

A serious adverse event (SAE) was defined as any untoward medical occurrence, whether or not related to the study product, experienced by a subject that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in a persistent or significant disability, or was a congenital anomaly/birth defect. Serious adverse events were required to be reported to the medical monitor within 24 hours of discovery. The monitor was to relay the information to the Sponsor immediately. The investigator had to inform the IRB/IEC within seven working days of the event. SAEs were followed by appropriate management until resolved. SAEs were collected from the time of the first dose until the subject had discontinued study medication and compassionate medication (if applicable) for 30 days.

Treatment-emergent adverse events (TEAEs) were defined as AEs experienced by the subject which occurred on or after Day 1 (first dose administered) through Day 15 or the Early Termination Visit. For subjects who continued to receive medication for compassionate use, TEAEs were collected for the 30 days following compassionate dispensation of the study drug. TEAEs that were considered most frequently occurring included events (in preferred term) reported in at least 5% of subjects in either treatment group.

Medical Officer's Comments:

The collection, recording, and reporting of adverse events in Study DIC-301 is standard and acceptable.

Primary Statistical Analyses:

Two analysis populations, consistent with the protocol, were defined as follows:

- Intent-to-Treat efficacy (ITT-E) population: Any subject who took at least one dose of study medication and had at least one post-baseline PUQE measurement.

- Intent-to-Treat safety (ITT-S) population: Any subject who took at least one dose of study medication during the study.

Two additional populations, subjects with complete data and per protocol subjects were used for sensitivity purposes for primary efficacy analysis.

- A subject with complete data was defined as a subject who: (a) had recorded baseline PUQE score, (b) had recorded PUQE scores for at least 7 of the 14 expected daily diaries from the second day of the subject's maximal dose taken to Day 15 (± 1 day), and (c) absence of any major protocol violations including the violation of entry criteria.

- A per protocol subject was defined as a subject who: (a) had a valid baseline assessment, (b) had recorded Day 15 (± 1 day) PUQE scores, (c) completed the study with between 80% to 120% of prescribed study medication applications, and (d) absence of any major protocol violations including the violation of entry criteria.

The efficacy analyses were conducted on ITT-E subject population. Safety analyses were conducted on the ITT-S subject population.

All statistical tests were two-sided using an alpha of 0.05 ($\alpha = 0.05$) in order to declare significance. An alpha level of 0.10 ($\alpha = 0.10$) was assumed to assess the significance of interaction effects when analyzing appropriate primary and secondary efficacy endpoints through analysis of variance (ANCOVA) or analysis of covariance (ANCOVA) models. Type III sums of square (SS) were used when evaluating ANOVA and ANCOVA models for between-group comparisons.

PUQE scores based on the ITT-E subject data via the last-observation-carried-forward (LOCF) method were evaluated using an analysis of covariance (ANCOVA) model where change from baseline to Day 15 (± 1 day) was the response variable, the baseline PUQE score was the covariate, and the treatment group and study center were the fixed effects. The following ANCOVA assumptions were tested at 5% significance level unless otherwise noted: (1) normality of errors, (2) homogeneity of variances, and (3) equality of slopes among treatment groups at 10% significance level. If the assumptions were severely violated, a nonparametric approach (rank-based analysis of covariance method) was used, stratifying by study center.

The primary efficacy analysis was performed for the ITT-E subject population.

Medical Officer's Comments:

Per the application, the PUQE tool "is a validated tool that measures the severity of symptoms of morning sickness. It records the severity of the 3 symptoms of NVP, nausea, vomiting and retching, their combination, as well as the overall well-being of the subject. Per the application, this tool is used clinically and in research. The external validity of PUQE has been assessed by examining its ability to predict several characteristics associated with NVP:

a) ability to take multivitamin supplements,
b) rates of hospitalization and emergency room visits for severe symptoms,
c) sleep pattern,
d) liquid intake and
e) the woman's self-rated Global Assessment of Well-Being scores."

Data collected prospectively from 315 women counseled by the Motherisk NVP line were used for the validation. Per the application, "PUQE showed strong correlation with all parameters examined except for sleep pattern and hydration status. The Global Assessment of Well-Being score, however, correlated significantly with hydration status. Additionally, the Spanish PUQE version has been validated for comprehensibility."[8]

As previously mentioned, the Motherisk NVP Healthline is a helpline of The Motherisk Program at the Hospital for Sick children, Toronto, Canada. It is a helpline developed to provide counseling to pregnant women experiencing nausea and vomiting of pregnancy. Women who contact the helpline receive counseling on strategies such as lifestyle changes, and receive advice about medication to manage NVP symptoms.

Per the application, change in each of the three individual components of the PUQE score (secondary endpoint) was compared between the two treatment groups using ANCOVA where change from Baseline to Day 15 (± 1 day) was the response variable, the Baseline value was the covariate, and the treatment group and study centers were the fixed effects. If the assumptions were severely violated, a nonparametric approach (rank-based analysis of covariance method) was to be used, stratifying by study center.

Change in the Global Assessment of Well-Being (secondary endpoint) was compared between the two treatment groups using ANCOVA where change from baseline to Day 15 (± 1 day) via LOCF was the response variable, the baseline value was the covariate, and the treatment group and study center were the fixed effects. If the assumptions were severely violated, a nonparametric approach (rank-based analysis of covariance method) was used, stratifying by study center.

8 Ebrahimi N, Maltepe C, Bournissen FG, Koren G. Nausea and Vomiting of Pregnancy: Using the 24-hour Pregnancy-Unique Quantification of Emesis (PUQE-24) Scale. J Obstet Gynaecol Can. 2009:31(9):803-807.

Number of tablets taken, total number of visits and phone calls to health care providers, and time loss from household tasks and/or employment (secondary endpoints) were analyzed using an analysis of variance (ANOVA) model where period total was the response variable and the treatment and study center were the fixed effects. If the assumptions (normality of errors and homogeneity of variances) were severely violated, a nonparametric approach (rank-based analysis of variance method) was used.

Compliance with study medication (0 = less than 28 tablets, 1 = 28 tablets, 2 = more than 28 tablets) and rates of hyperemesis gravidarum were examined using the Cochran-Mantel-Haenszel (CMH) row mean scores test controlling for study center.

Per the application, the expected difference in the PUQE scores between Diclegis and placebo is 3 (95% CI: 1- 5); therefore, for this study, 280 subjects (140 subjects per treatment group) were to be enrolled to achieve 200 evaluable subjects. An estimated dropout rate of 25% and a non-compliance rate of approximately 5% were expected. This sample size was at least 4-fold larger than needed to show the intended clinical effect.

The PUQE score based on 1) subjects with complete data via LOCF and 2) per protocol subjects were similarly performed separately for sensitivity purposes to examine the impact of missing data and data imputation.

Exploratory analyses were performed designed to investigate the relationship between levels of vitamin B_6 (total and metabolites) and doxylamine and the severity of NVP symptoms (PUQE score).

Safety Analyses:

All adverse events (AEs) collected were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 10.0 or higher), classified by system organ class (SOC) and preferred term (PT).

Treatment-emergent adverse events (TEAEs) were defined as AEs experienced by the subject which occurred on or after Day 1 (first dose administered) through Day 15 or the Early Termination Visit. For subjects who continued to receive medication for compassionate use, TEAEs were collected for the 30 days following compassionate dispensation of the study drug, thereafter only SAEs were collected during compassionate use. TEAEs that were considered most frequently occurring included events (in preferred term) reported in at least 5% of subjects in either treatment group.

TEAEs were tabulated by treatment group, SOC, PT, relationship, and severity. Summary tables for the Diclegis and placebo treatment groups were presented by tabulating the frequency of subjects with one or more TEAEs during the study and

compared using Pearson's Chi-square test or Fisher's exact test, if more appropriate, to examine the statistical significance of differences in TEAE rates. In addition, summarization by SOC and PT was provided for most frequently occurring TEAEs and SAEs. At each level of summarization (SOC or PT), subjects reporting more than one TEAE were only counted once under the strongest relationship and/or severity.

In addition, the relationship of TEAEs to plasma levels of vitamin B_6 (total and each metabolite) and doxylamine were evaluated using a logistic regression. The response variable was defined as whether the subject had a TEAE of interest, the explanatory variables (covariates) included treatment group and each plasma level of vitamin B6 or doxylamine. The mean values of each plasma level of vitamin B6 and doxylamine of Day 4, 8, and 15 were used. The analysis was conducted on the most frequently occurring TEAEs (5% or greater of total subjects) for each SOC and PT

Protocol Amendments for Study DIC-301:

The original protocol for Phase 3 Study DIC-301 was submitted to IND 72300 on December 21, 2006. The first subject enrollment in Study DIC-301 was on February 7, 2008. The last subjects completed Study DIC-301 on June 16, 2009. In total, 4 amendments were submitted to the original 2006 protocol:

Amendment 1 dated March 27, 2007 reduced the number of study sites, increased the PUQE eligibility requirement score (PUQE score > 4 was increased to PUQE score ≥ 6), reduced the requirement for post-baseline PUQE measurements (from twice daily, am and pm, to once daily in the morning at approximately the same time each day), revised text to correct inconsistencies and accurately reflect revisions to the statistical portions of the protocol, added drug accountability at each visit, improved schedule of events footnotes for clarity, readability, the 24 hour score, revised text to accurately reflect the current version of the Global Assessment of Well-Being used and the days on which it was performed, revised compassionate use to include AE collection within the first 4 weeks after the end of study, corrected procedural and statistical errors, and revised the schedule for blood sample collection to allow for greater flexibility.

Amendment 2 dated June 7, 2007 defined the vitamin B_6 metabolites to be evaluated, changed clinic evaluations from midday to morning, removed age restrictions as an inclusion criterion (changed from "pregnant female equal to or greater than 18 years old" to "patient is a pregnant female"), clarified treatments excluding subjects from study participation, clarified scheduling and content of PUQE evaluation and diary completion, added a serum chemistry analyte, and allowed for down-titration of study drug in the case of related AEs.

Amendment 3 dated September 13, 2007 added back the minimum age criterion for study inclusion ("pregnant female equal to or greater than 18 years old"), clarified schedule of events, changed the Global Assessment of Well-Being scale, clarified days

of diary recording, determined that subjects were required to have a clinic visit every 4 weeks during compassionate use, and clarified wording of the Global Assessment of Well-Being questionnaire.

Amendment 4 dated May 20, 2008 clarified dosing procedures, allowing for subjects to take additional study drug if their symptoms of nausea and vomiting (PUQE score above 3) were not controlled by standard study drug administration (2 tablets), and increased the total subject number from 260 to 280 to account for non-compliance and drop-out subjects.

The final Clinical Study Report for Study DIC-301 is dated January 18, 2010.

6 Review of Efficacy

6.1 Indication

The proposed indication in the application reads, “Diclegis is indicated for the treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management.”

6.1.1 Methods

The data presented in the single, 15-day, safety and efficacy Phase 3 study (Study DIC-301) was reviewed in its entirety. Approximately 280 subjects (140 subjects per treatment group) were to be enrolled in the single primary 15-day Study DIC-301 in order to achieve 200 evaluable subjects. In Study DIC-301, there were 256 subjects in the Intent-to-Treat efficacy population (ITT-E) and 261 subjects in the Intent-to-treat safety population (ITT-S).

In addition, the following information presented in the application was reviewed in its entirety:

1. Limited safety and efficacy data presented in the 505(b)(2) application from the 1956 approved Bendectin® (10 mg doxylamine succinate, 10 mg pyridoxine hydrochloride, and 10 mg dicyclomine hydrochloride) application. Bendectin® was voluntarily removed from the market for non-medical reasons by the manufacture Merrell Dow in 1983.
2. Limited safety and efficacy data presented in this 505(b)(2) application from the 1975 reformulated Bendectin® containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride application. This information includes the FDA Review of

an "8-way" study that supported the approval of the re-formulated Bendectin® on November 4, 1976.

6.1.2 Demographics

Demographic and Baseline characteristics for the ITT-S population are summarized in Table 4.

Table 4: Demographics for Study DIC-301; Intent-to-Treat Population

Parameter and Statistic	Diclegis N = 133	Placebo N = 128	Total N = 261
Age (Years)			
N	132	128	260
Mean (SD)	25.9 ± 6.0	25.0 ± 5.6	25.5 ± 5.8
Median	25.0	23.5	24.0
(Min, Max)	(18, 45)	(18, 42)	(18, 45)
Body Mass Index (kg/m^2)			
N	133	128	261
Mean (SD)	28.88 ± 7.61	29.79 ± 11.13	29.32 ± 9.49
Median	28.00	26.86	27.46
(Min, Max)	(16.7, 53.2)	(11.6, 116.8)	(11.6, 116.8)
Weight (kg)			
N	133	128	261
Mean (SD)	74.35 ± 22.39	76.41 ± 22.33	75.38 ± 22.34
Median	69.85	68.72	68.95
(Min, Max)	(40.6, 163.4)	(44.9, 157.3)	40.6, 163.4)
Race			
N	133	128	261
African-American	50 (37.6%)	49 (38.3%)	99 (37.9%)
Caucasian	80 (60.2%)	75 (58.6%)	3 (1.1%)
Asian	2 (1.5%)	1 (0.8%)	155 (59.4%)
Other	1 (0.8%)	3 (2.3%)[a]	4 (1.5%)[a]
Gestational Age at Start of NVP symptoms (Weeks)			
N	132	128	260
Mean (SD)	5.5 ± 1.8	5.3 ± 1.8	5.4 ± 1.8
Median	5.0	5.0	5.0
(Min, Max)	(2, 10)	(0, 11)	(0, 11)
Gestational Age at Enrollment (Weeks)			
N	133	128	261
Mean (SD)	9.3 ± 1.9	9.3 ± 1.8	8.3 ± 1.9
Median	9.0	9.0	9.0
(Min, Max)	(7, 13)	(7, 14)	(7, 14)
PUQE score at Enrollment			
N	133	128	261
Mean (SD)	9.0 ± 2.1	8.8 ± 2.1	8.8 ± 2.1

Median (Min, Max)	9.0 (6, 15)	8.0 (5, 15)	8.0 (5, 15)

Source: Adapted from NDA 21876, Clinical Study Report, Table 10.2, page 43 of 84 and Table 10.3, page 44 of 84.
a. Includes Other and Not Reported.
Definitions: SD = standard deviation, Min = minimum, Max = maximum.

Medical Officer's Comments:

As shown in Table 4, the demographic data between treatment groups in Study DIC-301 were similar. Overall, in the two treatment groups, subjects were approximately the same age (median age of 24), developed NVP at approximately the same time (median 5.0 weeks of gestation), and were the same number of weeks of gestation at enrollment (median 9.0 weeks of gestation). Approximately 60% of study participants were Caucasian (155 of 261 subjects, 59.4%) and 38% of subjects were African-American (99 of 261 subjects). The inclusion of 38% African-American subjects in this study is commendable.

6.1.3 Subject Disposition

Of the 280 subject enrolled into Study DIC-301, only 261 subjects received study medication (19 subjects did not receive study medication: 7 in the Diclegis treatment group [5.0%] and 12 in the placebo treatment group [8.6%]). Overall, 203 subjects completed Study DIC-301 (72.5%, 203 of 280 enrolled subjects). More Diclegis-treated subjects completed Study DIC-301 (80.0%, 112 of 140 randomized subjects) than placebo-treated subjects 65.0%, 91 of 140 randomized subjects). See Table 5.

Table 5: Final Study Disposition for Study DIC-301

Subject Disposition	Diclegis N (%)	Placebo N (%)	Total N (%)
Subjects Randomized	140 (100%)	140 (100%)	280 (100%)
Subjects in ITT-S Population[1]	133 (95.0%)	128 (91.4%)	261 (93.2%)
Subjects in ITT-E Population[2]	131 (93.6%)	125 (89.3%)	256 (91.4%)
Subjects Completed Study[2]	112 (80.0%)	91 (65.0%)	203 (72.5%)
Subjects Discontinued Study[2]	28 (20.0%)	49 (35.0%)	77 (27.5%)
Reasons Discontinued			
- Adverse Event	5 (3.6%)	5 (3.6%)	10 (3.6%)
- Subject Withdrew Consent	9 (6.4%)	18 (12.9%)	27 (9.6%)
- Investigator Discretion	2 (1.4%)	1 (0.7%)	1 (0.4%)
- Treatment Failure	2 (1.4%)	5 (3.6%)	7 (2.5%)
- Lost to Follow-up	7 (5.0%)	19 (13.6%)	26 (9.3%)
- Other	5 (3.6%)	1 (0.7%)	6 (2.1%)

Source: Adapted from NDA 21876, Clinical Study Report, Table 10.1, page 41 of 84.
[1] The denominator is the number of subjects enrolled.
[2] The denominator is the number of subjects randomized
Definitions: ITT-S = Intent-to-treat safety; ITT-E = Intent-to-treat efficacy.

Medical Officer's Comments:

As shown in Table 5, 15% more subjects in the placebo treatment group discontinued Study DIC-301 than in the Diclegis treatment group. The most common reasons for discontinuation in the placebo treatment group in order of frequency, and higher than the Diclegis treatment group, were: lost to follow-up (13.6%, 10 of 140 randomized subjects), subject withdrew consent (12.9%, 18 of 140 randomized subjects), treatment failure (3.6%, 5 of 140 randomized subjects), and Investigator discretion (0.7%, 1 of 140 randomized subjects). Discontinuation rates were similar between the two treatment groups for adverse events as the reason for discontinuation (3.6%, 5 subjects in each treatment group), however. The increased discontinuation rate in the placebo treatment group over the active treatment group in Study DIC-301 is not unexpected.

Also shown in Table 5, a total of 19 randomized subjects received no study medication (7 subjects in the Diclegis treatment group [5.0%] and 12 in the placebo treatment group [8.6%]), and were excluded from the ITT-S analysis. A total of 24 subjects were excluded from the efficacy analysis because they had no post-baseline PUQE score (9 subjects in the Diclegis treatment group [6.4%] and 15 subjects in the placebo treatment group [10.7%]).

6.1.4 Analysis of Primary Endpoint(s)

In Study DIC-301, the primary efficacy endpoint was the change from baseline in the PUQE score at Day 15 (± 1 day). Change from baseline was calculated as post-baseline score minus baseline value. The PUQE score incorporates the number of daily vomiting episodes, number of daily heaves, and length of daily nausea in hours, for an overall score of symptoms rated from 3 (no symptoms) to 15 (most severe symptoms). Baseline was defined as the PUQE score completed at the enrollment visit.

PUQE scores based on the ITT-E subject data via the last-observation-carried-forward (LOCF) method were evaluated using an analysis of covariance (ANCOVA) model where change from Baseline to Day 15 (± 1 day) was the response variable, the Baseline PUQE score was the covariate, and the treatment group and study center were the fixed effects. The following ANCOVA assumptions were tested at 5% significance level unless otherwise noted:

(1) normality of errors,
(2) homogeneity of variances, and
(3) equality of slopes among treatment groups at 10% significance level.

If the assumptions were severely violated, a nonparametric approach (rank-based analysis of covariance method) was used, stratifying by study center.

The following four populations were pre-specified in the study protocol:

- ITT-S: Any subject who took at least one dose of study medication during Study DIC-301.
- ITT-E: Any subject who took at least one dose of study medication and had at least one post-baseline PUQE measurement.
- Completed data: Any subject who: (a) has recorded baseline PUQE score, (b) has recorded PUQE score for at least 7 of the 14 expected daily diaries from the second day of the subject's maximal dose taken to Day 15 (± 1 day), and (c) absence of any major protocol violations including the violation of entry criteria.
- Per protocol (PP): Any subject who: (a) has a valid baseline assessment, (b) has recorded Day 15 (± 1 day) PUQE scores, (c) completed the study with between 80% - 120% of prescribed study medication applications, and (d) absence of any major protocol violations including the violation of entry criteria.

The Statistical Reviewer for NDA 21876 defined one addition study population for Study DIC-301 to include any subject who completes the study without excluding subjects with protocol violations:

- Completed study: Any subject who: (a) has recorded baseline PUQE score and (b) has recorded PUQE score for at least 7 of the 14 expected daily diaries from the second day of the subject's maximal dose taken to Day 15 (± 1 day).

The efficacy analyses were conducted on the ITT-E subject population.

Sensitivity analyses were done to examine the impact of missing data and data imputation, and hence to determine that study conclusions were invariant to assumptions, the particular model, and methods of handling missing data. The subjects with complete data and the PP subjects were used for sensitivity purposes for the primary efficacy analysis. The Statistical Reviewer also conducted a sensitivity analysis using the completed study population.

Per the application, two additional exploratory analyses were generated after the database lock:

1. Summarization of the relationship between change from baseline in PUQE score on Day 15 and average plasma levels of clinical visits for the ITT-E population.
2. Summarization of the number of subjects per treatment group who requested to continue receiving study drug at the end of the 15 day trial.

A statistically significant difference between Diclegis versus placebo, as measured by the PUQE score between Baseline and Day 15, was demonstrated in Study DIC-301. See Table 6.

Table 6: Primary Efficacy Analysis: Change from Baseline to Day 15 (± 1 day) in the PUQE Score for the Intent-to-Treat Population (Applicant's ITT-E); LOCF

Data/Category - Statistics	**Diclegis Treatment Group (N = 131)**	**Placebo Treatment Group (N = 125)**
Baseline		
- Mean ± SD	9.0 ± 6.1	8.8 ± 2.1
- Median	9.0	8.0
- (Min, Max)	(6, 15)	(6, 15)
Day 15 (± 1 day)		
- Mean ± SD	4.2 ± 1.9	4.9 ± 2.3
- Median	3.0	4.0
- (Min, Max)	(3, 11)	(3, 12)
Change from Baseline		
- Mean ± SD	-4.8 ± 2.7	-3.9 ± 2.6
- Median	-5.0	-4.0
- (Min, Max)	(-11, 3)	(-11, 2)
P value for Comparison	0.006[1]	-

Source: Adapted from NDA 21876; Clinical Overview, Table 1.5-6, page 24 of 61; and Clinical Study Report, Table 11.1, page 47 of 84.

1. P-value for treatment comparison (Diclegis versus placebo) from rank-based analysis of variance stratified by center.

Definitions: LOCF = last observation carried forward, SD = standard deviation, Min = minimum, max = maximum.

Medical Officer's Comments:

As shown in Table 6, there was a statistically significantly larger mean decrease (thereby indicating improvement in symptoms) in the 15-Day PUQE score for the Diclegis treatment group (-4.8 ± 2.7) than the placebo treatment group (-3.9 ± 2.6) for the ITT-E/LOCF population. The Diclegis treatment group demonstrated a statistically significant improvement in the PUQE score versus the placebo treatment group at Day 15 (p=0.006).

In the NDA application, however, the Applicant did not provide a point estimate of the treatment difference between Diclegis and placebo and its 95% confidence interval (CI) for the PUQE score and the 3 individual components of the PUQE score. Therefore, an information request was sent to the Applicant on November 8, 2012. The Applicant responded on December 5, 2012 and provided the following information. See Table 7.

Table 7: Change from Baseline to Day 15 (± 1 day) in the PUQE Score and its Three Components (ITT-E Population via LOCF)

Population	Diclegis N = 131	Placebo N = 125	Diclegis vs. Placebo	
	Change from Baseline	Change from Baseline	Difference (95% CI)	p-value
PUQE score	-4.67	-3.94	-0.73 (-1.24, -0.22)	0.006
Hours of nausea	-2.35	-2.13	-0.21 (-0.49, 0.06)	0.125
Number of times Vomited	-0.95	-0.72	-0.23 (-0.39, -0.06)	0.008
Number of Retching Episodes	-1.37	-1.1	-0.28 (0.46, -0.09)	0.003

Source: Adapted from NDA 21876, Applicant's response to November 8, 2012 request for information and Table 5 in the Statistical Review.
Definitions: ITT-E = Intent-to-treat – efficacy, LOCF = last observation carried forward, CI = confidence interval.

Medical Officer's Comments:

The Statistical reviewer confirmed the analyses presented in Table 7 with some minor differences. In the Statistical reviewer's analysis, the difference between Diclegis vs. placebo is -0.73 (-1.25, -0.22), the p-value for hours of nausea is p=0.126, and the p-value for number of retching episodes is p=0.004.

A small treatment improvement over placebo in the PUQE score of -0.73 (95% CI, -1.24 to -0.22) is shown in Table 7 that is statistically significant (p=0.006). In addition, Table 7 demonstrates a statistically significant improvement in 2 of the 3 individual components of the PUQE score: number of times vomited (p=0.008) and number of retching episodes (p=0.003). The reduction in the number of hours of nausea was not statistically different from placebo (p=0.125). However, the protocol pre-specified that the mean change in the PUQE score, between Baseline and Day 15, was the primary endpoint for Study DIC-301. DRUP concurred with this primary endpoint.

Efficacy Results Available for the RLD Bendectin®:

In support of efficacy of the combination of 10 mg doxylamine and 10 mg pyridoxine, the Applicant includes in the NDA application a 1975 FDA Review of a randomized, double-blind, multi-center, placebo-controlled study of Bendectin® conducted in 2,308 women with NVP under IND (b) (4). Various single dose treatment and combinations of 10 mg doxylamine, 10 mg dicyclomine hydrochloride, and 10 mg of pyridoxine were compared with placebo over 7 days in an 8-way study design. Treatment groups included:

1) Bendectin® 1956 original formulation (10 mg doxylamine and 10 mg dicyclomine HCL and 10 mg pyridoxine)
2) 10 mg doxylamine and 10 mg pyridoxine

3) 10 mg dicyclomine HCL and 10 mg doxylamine
4) 10 mg doxylamine alone
5) 10 mg dicyclomine HCL and 10 mg pyridoxine
6) 10 mg pyridoxine alone
7) 10 mg dicyclomine HCL alone
8) Placebo

Each subject was instructed to take 2 tablets at bedtime for 7 nights, and if necessary 1 additional tablet in the morning and/or mid-afternoon. Evaluations (not specifically defined in the report document) by the investigator were performed at the initial visit and again following completions of the 7 days of treatment. Subjects completed a diary card at baseline and on each study day. Efficacy was evaluated and included: 1) hours of nausea as reported on the diary card, 2) frequency of vomiting as reported on the diary card, and 3) an overall effectiveness of medication judgment completed by the investigator. Per the information provided, a total of 1599 subjects with nausea and/or vomiting reported that they took medication on each of the 6 successive study days and supplied diary cards on each of these 6 days. Adverse reactions volunteered by the subject were recorded.

Two efficacy tables are provided in this 1975 FDA Review, one summary table for the physician's evaluation and one summary table for the subject's diary card. The reported results are demonstrated in the following 2 tables.

Table 8: Summary Table; Physician Evaluation

Treatment	Effectiveness of Medication		Nausea		Vomiting[1]	
	Percentage evaluated as moderate or excellent	P[2]	Percentage improved	P	Percentage improved	P
Bendectin®	71	<.01	65	<.01	77	.03
Doxylamine and pyridoxine	78	<.01	75	<.01	73	.17
Dicyclomine and doxylamine	78	<.01	71	<.01	74	.07
Doxylamine	77	<.01	69	<.01	78	.01
Dicyclomine and pyridoxine	61	.28	57	.03	62	.64
Pyridoxine	66	.10	68	<.01	66	.36
Dicyclomine	61	.17	61	.07	71	.33
Placebo	57	-	52	-	66	-

Source: Adapted from NDA 21876, Clinical Overview, 1975 FDA Review dated 3/14/75.
[1] The analysis of vomiting includes only those patients with vomiting symptoms pretreatment.
[2] The p values are one sided probabilities based on tests of each active medication vs. placebo.

Table 9: Summary Table; Patient's Diary Card

Treatment	Nausea		Vomiting[1]	
	Percent reduction from pretreatment	P[2]	Percentage with no vomiting on 5 or more treatment days	P
Bendectin®	57	<.01	46	<.01
Doxylamine and pyridoxine	64	<.01	48	<.01
Dicyclomine and doxylamine	50	<.01	49	<.01
Doxylamine	56	<.01	54	<.01
Dicyclomine and pyridoxine	44	.03	39	.08
Pyridoxine	35	.09	29	.08
Dicyclomine	36	.25	30	.26
Placebo	31	-	28	-

Source: Adapted from NDA 21876, Clinical Overview, 1975 FDA Review dated 3/14/75.
[1] The analysis of vomiting includes only those patients with vomiting symptoms pretreatment.
[2] The p values are one sided probabilities based on tests of each active medication vs. placebo.

Medical Officer's Comments:

The FDA reviewer, who prepared the review of this 1975 study, provides the following comments:

"The control of nausea by doxylamine alone and by each of the 3 combination which contain doxylamine was consistently statistically significantly (p<0.01) superior to placebo by both physician's records and patient's records. Additionally, the control of vomiting favored all formulations containing doxylamine by a statistical significance, as compared to placebo, of p<0.01 by the patient's records and in 2 of the 4 doxylamine formulations (i.e., doxylamine alone and Bendectin) of p≤0.03 by the physician's records. By factorial analysis, all medications with doxylamine alone or in combination (4 medications) were, by physician's records and patient's records, more effective in controlling nausea and vomiting than those which did not contain this ingredient (4 medications) with a statistical probability of <0.01"

"Pyridoxine alone excelled over placebo (p<0.01) in the reduction of nausea as demonstrated by physician's records; the patient's records of nausea favored pyridoxine with p=0.09. Greater efficacy for treatment of nausea by doxylamine/pyridoxine over doxylamine alone was supported marginally with p values of 0.12 and 0.26 by the patient's records and physician record's, respectively. Factorial analysis of the 4 medications with vs. without pyridoxine indicated effectiveness in the control of nausea with p values of 0.01 by patient's records and 0.08 by physician' records."

"Dicyclomine alone had marginal efficacy over placebo by both physician's records and patient's records in the treatment of nausea (p=0.07 by physician's records; p=0.25 by patient's records). Dicyclomine combined with pyridoxine was superior to placebo

(p=0.03) for control of nausea by both patient's records and physician's evaluations. The contribution of dicyclomine to the efficacy of dicyclomine to the efficacy of doxylamine when given in combination was not measurable in this study."

The 1975 FDA Review, concludes, but is not limited to, the following:

1. *"This "8-way" study confirms the previous findings that Bendectin is effective in the control of nausea and vomiting of pregnancy.*
2. "*This "8-way" study confirms the previous findings that doxylamine and the combinations containing doxylamine (including Bendectin) are effective in the control of nausea and vomiting of pregnancy.*"
3. *"The rationale for providing pyridoxine as a nutritional supplement during pregnancy and in the dosage employed, plus the evidence of its efficacy for control of nausea as well as its contribution to the efficacy of the combination as demonstrated in this study, indicates that pyridoxine is a clinically important component of the anti-nausea/anti-emetic product, Bendectin."*

Based on the Agency's finding of effectiveness for Bendectin® (reformulated two components of 10 mg doxylamine and 10 mg pyridoxine), this data can be used in support of the effectiveness of Diclegis (10 mg doxylamine and 10 mg pyridoxine) in the treatment of NVP.

In an Agency's Federal Register Notice dated July 29, 1977 (Volume 42, No. 146) regarding the removal of dicyclomine hydrochloride for the original Bendectin® formulation, supplementary information provided states that, "Merrell National Laboratories had earlier supplemented their new drug application to provide for a reformulated product containing only doxylamine succinate and pyridoxine hydrochloride, which was approved on November 4, 1976, through the normal supplemental new drug application procedures."

Medical Officer's Comments:

The November 4, 1976 approval of the reformulated Bendectin® including only 10 mg doxylamine and 10 mg pyridoxine was based on the reported findings in the 1975 "8-way" study.

In the application, the Applicant also includes the reported results of the FDA 1975 study in support of the effectiveness of Diclegis to treat NVP. The following illustration, representing the (b) (4) is included in the application and is proposed, by the Applicant, for inclusion in the Diclegis labeling.

(b) (4)

Medical Officer's Comments:

As previously noted, this reviewer concurs that the data from the 1975 "8-way" study supports the effectiveness of Diclegis in the treatment of NVP. (b) (4)

The Applicant also includes the following table in the application and in their proposed Diclegis labeling, in support of the effectiveness of Diclegis to treat NVP, which incorporates the (b) (4)

(b) (4)

Medical Officer's Comments:

(b) (4)

In a final statement regarding the effectiveness of Diclegis to treat NVP, this reviewer notes that the Agency states in a 1999 Federal Register Notice (Volume 64, No. 152, August 9, 1999): "The agency has reviewed information submitted with the petitions, published studies, U.S. and foreign adverse events reports, and FDA records. The current evidence supports the conclusion that Bendectin was not withdrawn from the market for reasons of safety or effectiveness."

Medical Officer's Efficacy Comments:

The primary efficacy results presented in the single, placebo-controlled 15-day study (Study DIC-301) support the approval of Diclegis (10 mg doxylamine and 10 mg pyridoxine) delayed release tablets for the treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management (p=0.006).

The efficacy results presented in the 1975 FDA Review of the RLD Bendectin® (10 mg doxylamine and 10 mg pyridoxine) support the findings in Study DIC-301.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy endpoints in Study DIC-301 included:

- the three individual components constituting the PUQE (hours of nausea, number of times vomiting, and number of times retching),
- Global Assessment of Well-Being,
- number of tablets taken,
- time loss from household tasks and/or employment,
- total number of visits and phone calls to healthcare providers,
- rates of hyperemesis gravidarum, and
- compliance with study medication (0 = less than 28 tablets, 1 = 28 tablets, 2 = more than 28 tablets).

Changes in each of the three individual components constituting the PUQE score was compared between the two treatment groups using ANCOVA where change from Baseline to Day 15 (± 1 day) was the response variable, the baseline value was the covariate, and the treatment group and study center were the fixed effects. If the assumptions were severely violated, a nonparametric approach (rank-based analysis of covariance method) was to be used, stratifying by study center.

Number of tablets taken, total number of visits and phone calls to healthcare providers, and time loss from household tasks and/or employment were analyzed using an analysis of variance (ANOVA) model where period total was the response variable and the treatment and study center were the fixed effects. If the assumptions (normality of errors and homogeneity of variances) were severely violated, a nonparametric approach (rank-based analysis of variance method) was used.

Compliance with study medication and rates of hyperemesis gravidarum were examined using the Cochran-Mantel-Haenszel (CMH) row mean scores test controlling for study center.

All secondary efficacy analyses were performed for the ITT-E population.

Individual Components of the PUQE Score:

Statistical analyses at Baseline and Day 15 (± 1 day) for the 3 individual components of the PUQE score with corresponding p-values for the ITT-E population are provided in Table 10.

Table 10: Secondary Efficacy Analysis: Change from Baseline to Day 15 (± 1 day) in PUQE Score Individual Components, ITT-E Population

Data/Category	Statistics	Diclegis N = 131	Placebo N = 125
Hours of Nausea			
Baseline	N	131	125
	Mean ± SD	4.0 ± 1.0	4.1 ± 0.9
	Median	4.0	4.0
	Min, Max	2, 5	2, 5
Day 15 (± 1 day)	N	110	75
	Mean ± SD	1.5 ± 1.0	1.6 ± 0.9
	Median	1.0	1.0
	Min, Max	1, 5	1, 5
Change from baseline	N	110	91
	Mean ± SD	-2.6 ± 1.2	-2.5 ± 1.1
	Median	-3.0	-3.0
	Min, Max	-4, 2	-4, 1
P-value for Comparison	-	0.649[a]	-
Number of Times Vomiting			
Baseline	N	131	125
	Mean ± SD	2.2 ± 12	2.1 ± 1.2
	Median	2.0	2.0
	Min, Max	1, 5	1, 5
Day 15 (± 1 day)	N	110	75
	Mean ± SD	1.1 ± 0.3	1.2 ± 0.5
	Median	1.0	1.0
	Min, Max	1, 2	1, 3
Change from baseline	N	110	91
	Mean ± SD	-1.1 ± 1.2	-0.8 ± 1.2
	Median	-1.0	0.0
	Min, Max	-4, 1	-4, 1
P-value for Comparison	-	0.084[a]	-
Number of Times Retching			
Baseline	N	131	125
	Mean ± SD	2.7 ± 1.1	2.6 ± 1.2
	Median	2.0	2.0

	Min, Max	1, 5	1, 5
Day 15 (± 1 day)	N Mean ± SD Median Min, Max	110 1.2 ± 0.5 1.0 1, 4	91 1.4 ± 0.7 1.0 1, 5
Change from baseline	N Mean ± SD Median Min, Max	110 -1.5 ± 1.2 -1.0 -4, 1	91 -1.3 ± 1.1 -1.0 -4, 2
P-value for Comparison	-	0.082[a]	-

Source: Adapted from NDA 21876, Table 14.4.2.1, 14.4.2.2, and 14.4.2.3.
a. P-values for treatment comparison (Diclegis vs. Placebo) from rank-based analysis of variance stratified by center.
Definitions: ITT-E = intent-to-treat – efficacy, SD = standard deviation, Min = minimum, Max = maximum.

Medical Officer's Comments:

As shown in Table 10, the individual mean PUQE component scores were comparable at baseline for the two treatment groups. Based on the analyses presented, the mean change for each of the three individual PUQE score components were similar for the two treatment groups, however, no statistically significant differences were demonstrated for any of the 3 individual components.

Global Assessment of Well-Being:

The mean change in the Global Assessment of Well-Being score for the ITT-E population from Baseline to Day 15 in the Diclegis treatment group increased from 5.0 ± 2.3 to 7.8 ± 2.2 ± (mean change from baseline 2.8 ± 2.8) versus an increase of 5.4 ± 2.2 to 7.2 ± 2.0 (mean change from baseline (1.8 ± 2.2) for placebo, and was statistically significantly higher than the mean change in the placebo group (p=0.005). See Table 11.

Table 11: Secondary Efficacy Analysis: Change from Baseline to Day 15 (± 1 day) in Global Assessment of Well-Being for the ITT-E Population

Data/Category	Statistics	Diclegis N = 131	Placebo N = 125
Baseline	N Mean ± SD Median Min, Max	130 5.0 ± 2.3 5.0 0, 10	125 5.4 ± 2.2 5.0 0, 10
Day 15 (± 1 day)	N Mean ± SD Median Min, Max	131 7.8 ± 2.2 8.0 0, 10	125 7.2 ± 2.0 8.0 0, 10
Change from baseline	N Mean ± SD Median Min, Max	130 2.8 ± 2.8 2.5 -5, 10	75 1.8 ± 2.2 2.0 -3, 9

P-value for Comparison	-	0.005[a]	-

Source: Adapted from NDA 21876, Table 14.4.3

a. P-values for treatment comparison (Diclegis vs. Placebo) from rank-based analysis of variance stratified by center.

Definitions: ITT-E = intent-to-treat – efficacy, SD = standard deviation, Min = minimum, Max = maximum.

Medical Officer's Comments:

In Study DIC-301, the mean Global Assessment of Well-Being score increased (indicating improvement in well-being) in both treatment groups. The increase in the Diclegis treatment group was statistically significantly greater than the placebo treatment group (p=0.005).

Number of Tablets Taken:

The mean number of tablets (SD) taken was similar for both treatment groups. In the Diclegis treatment group, 36.6 ± 13.3 tablets were taken versus 34.0 ± 15.1 tablets taken in the placebo treatment group. As previously noted in this review, the minimum assigned study medication was 2 tablets daily at bedtime. One additional tablet could be taken in the morning, and a fourth tablet could be taken mid-afternoon to treat persistent NVP. While all subjects received 2 tablets before sleep, thereafter the dosage schedule was individualized according to the timing, duration, severity, and frequency of the symptoms experienced by the subject.

In Study DIC-301, the proportion of subjects who took the required 28 tablets was greater for the Diclegis treatment group (8.4%, 11 of 131 subjects) than for the placebo treatment group (4.8%, 6 of 125 subjects). Conversely, the proportion of subjects taking fewer than 28 tablets was lower in the Diclegis treatment group (23.7%, 31 of 131 subjects) than for the placebo treatment group (30.4%, 38 of 125 subjects). However, the remaining subjects in each treatment group similarly took more than 28 tablets (67.9% [89 of 131 subjects] in the Diclegis treatment group and 64.8% [81 of 125 subjects] in the placebo treatment group]). None of these reported differences between the two treatment groups were statistically significant (p=0.283).

Medical Officer's Comments:

In Study DIC-301, a small proportion of subjects in both treatment groups took only the required 28 tablets (8.4%, 11 of 131 Diclegis-treated subjects and 4.8%, 6 of 125 placebo-treated subjects). The majority of subjects in Study DIC-301 experiencing symptoms of NVP required more than 28 tablets (2 per night) of study medication (67.9%, 89 of 131 Diclegis-treated subjects and 64.8%, 81 of 125 placebo-treated subjects).

On February 22, 2013, the Applicant was requested to provide the following information:

"For the primary endpoint PUQE and its 3 components constituting the PUQE, please provide the following subgroup analyses. In addition to p-value, point estimate of treatment difference between Diclectin and Placebo and its 95% confidence interval should be provided:

1. Subgroup analysis by total number of tablets taken during the 15-day study (less than 28, 28 total or more tablets).
2. Subgroup analysis by gestation age at start of NVP symptom (etc: < 8 weeks; weeks 8 to 12; and > 12 weeks or any other grouping you feel appropriate).

Datasets used in the above analyses and SAS programs related to the analyses listed above should also be provided. These programs should be sufficient to duplicate your results."

Medical Officer's Comments:

The information requested is of interest to this reviewer. Approximately 30% of subjects were "satisfied" with the effectiveness of 28 or less tablets and, therefore, did not need either an additional morning or midafternoon tablet to control her symptoms.

Likewise, a subgroup analysis by gestational age is of interest to this reviewer. For inclusion in Study DIC-301, a gestational age between 7 to 14 weeks was required. However, NVP often presents with less severity at or shortly after the end of the first trimester (12 weeks gestation).

Time Loss from House Task and/or Employment:

The mean (± SD) time loss from household tasks was similar for both treatment groups in Study DIC-301 (6.09 ± 15.54 hours for Diclegis versus 5.51 ± 12.83 hours for placebo), and were not statistically significantly different (p=0.885)

There was a trend toward more loss of work in the placebo treatment group with a mean of 2.37 ± 10.23 hours versus 0.92 ± 3.86 hours in the Diclegis treatment group. The difference was not statistically significant (p=0.064).

Visits and Telephone Calls to Healthcare Providers:

In Study DIC-301, the mean (± SD) number of visits to healthcare providers was similar for both treatment groups (0.1 ± 0.5 visits for Diclegis versus 0.1 ± 0.3 for placebo), and not statistically significantly different (p=0.885).

The mean number of phone calls to healthcare providers was also similar for both treatment groups (0.1 ± 0.4 phone calls for Diclegis versus 0.1 ± 0.3 for placebo), and not statistically significantly different (p=0.581).

Rates of Hyperemesis Gravidarum:

No subjects in Study DIC-301 developed hyperemesis gravidarum.

Compliance with Study Medication:

In Study DIC-301, the difference in the study drug compliance between the two treatment groups was not statistically significant (p=0.283):

- 8.4% of Diclegis-treated subjects versus 4.8% of placebo-treated subjects took 28 tablets
- 23.7% of Diclegis-treated subjects versus 30.4% of placebo-treated subjects took fewer than 28 tablets
- 67.9% of Diclegis-treated subjects versus 64.8% of placebo-treated subjects took more than 28 tablets
-

Overall, 29 Diclegis-treated subjects (20.7%) and 48 (34.3%) placebo-treated subjects were outside 80 to 120% treatment compliance.

Medical Officer's Comments:

As noted previously, the increase in the Diclegis treatment group was statistically significantly greater than the placebo treatment group (p=0.005) in the mean Global Assessment of Well-Being score, one of the multiple secondary endpoints in Study DIC-301. However, except for the reported results of the Global Assessment of Well-Being, none of the changes observed in the other secondary endpoints showed statistically significant differences.

6.1.6 Other Endpoints

After database lock, the applicant performed two additional analyses:

1. Summarization of the relationship between change from baseline in PUQE score on Day 15 and average plasma levels of clinical visits for the ITT-E population.

2. Summarization of the number of subjects per treatment group who requested to continue receiving study drug at the end of the 15 day trial.

The metabolites of vitamin B_6 (pyridoxine, pyridoxal, and pyridoxal 5'-phosphate) were measured by blood sample drawn in the morning prior to the morning study dose using LC/MS/MS methods to represent steady state trough levels on Day 4 (± 1 day), Day 8 (± 1 day), and Day 15 (± 1 day). Total vitamin B_6 concentrations were calculated by

adding the concentrations of pyridoxine, pyridoxal, and pyridoxal 5'-phosphate for each sampling time for every subject.

The change in baseline PUQE score was correlated with plasma levels of vitamin B_6 (total and metabolites) and doxylamine on Day 4 (± 1 day), Day 8 (± 1 day), and Day 15 (± 1 day) using the Pearson correlation coefficient, and the associated p-value provided. These analyses were performed for the dosed subjects in the ITT-E subject population. See Table 12.

Table 12: Exploratory Efficacy Analysis: Relationship Between Change from Baseline in the PUQE Score and Plasma Levels of Doxylamine and Pyridoxine for ITT-E Population – Dosed Subjects Only

			Plasma Level of Vitamin B_6				
Visit	Statistics	Change from Baseline in PUQE Score	Pyridoxine	Pyridoxal 5' -Phosphate	Pyridoxal	Doxylamine	Total Vitamin B_6
DAY 4	N	126	117	121	120	121	121
	Mean± SD	-3.6 ± 2.6	0.946 ± 4.252	47.221 ± 21.703	15.559 ± 29.804	66.032 ± 33.598	63.567 ± 44.839
	Median	-4.0	0.000	44.720	10.790	70.680	55.650
	Min,Max	-11, 4	0.00, 32.78	6.50, 127.42	0.00, 255.55	0.00, 152.43	6.50, 365.50
	PCC(P-value)[1]		-0.090(0.340)	-0.015(0.871)	0.062(0.502)	-0.113(0.222)	0.024(0.793)
DAY 8	N	120	107	113	110	112	113
	Mean± SD	-4.6 ± 2.6	2.432 ± 17.832	53.379 ± 23.909	21.073 ± 26.162	75.152 ± 46.570	76.195 ± 53.206
	Median	-5.0	0.000	53.700	16.445	72.660	71.870
	Min,Max	-11, 3	0.00, 179.96	5.13, 107.83	0.00, 186.83	0.00, 196.53	5.13, 448.60
	PCC(P-value)[1]		0.187(0.055)	-0.070(0.466)	0.119(0.219)	-0.120(0.210)	0.092(0.333)
DAY 15	N	101	120	120	120	120	121
	Mean± SD	-5.2 ± 2.5	0.861 ± 4.817	44.968 ± 25.741	20.005 ± 32.904	61.844 ± 52.802	65.290 ± 52.706
	Median	-5.0	0.000	42.440	11.820	60.105	57.610
	Min,Max	-11, 3	0.00, 38.45	4.77, 126.28	0.00, 214.71	0.00, 200.38	4.77, 297.20
	PCC(P-value)[1]		0.019(0.849)	-0.007(0.947)	0.182(0.072)	-0.114(0.263)	0.106(0.293)

Source: Adapted from NDA 21876, Table 14.4.6, page 49 of 84.

Medical Officer's Comments:

There is no apparent relationship between vitamin B_6 levels (and metabolites) and doxylamine and the change from baseline PUQE scores on the Day 4, Day 8, or Day 15 visits. However, there is high variability in the data presented in Table 12, since most of the data points (> 50%) are detected as zero, especially for pyridoxine due to its short half-life. Overall, the exposure-response analysis could not demonstrate any correlation between change in the PUQE score and doxylamine and pyridoxine/metabolites.

Per the application, sixty-four (64) of Diclegis-treated subjects (48.9%) and 41 of placebo-treated subjects (32.8%) requested to continue study medication (p=0.009) at the completion of Study DIC-301 in this analysis performed after database lock.

Medical Officer's Comments:

Although this analysis was performed after database lock, the results of this analysis indicates to this reviewer that the Diclegis treatment effect was clinically meaningful to the women in the Diclegis treatment group.

6.1.7 Subpopulations

No subpopulations were analyzed in Study DIC-301 in the application.

The Statistical reviewer, however, prepared a subgroup analysis by race as shown in Table 13.

Table 13: Primary Endpoint Analysis: Change from Baseline to Day 15 (± 1 day) in PUQE Score by Race (ITT-E Population)

Population	Diclectin		Placebo		Diclectin vs. Placebo	
	n	Change from Baseline	n	Change from Baseline	Diff. (95% C.I.)	p-value
White	80	-4.59	73	-4.01	-0.58 (-1.28, 0.11)	0.101
African American	49	-4.96	48	-3.89	-1.06 (-1.88,-0.25)	0.010

Source: Statistical Reviewer's Analysis of NDA 21876, Table 9, page 13.
Definitions: ITT-E = intent-to-treat – efficacy; CI = confidence interval.

Medical officer's Comments:

As shown in Table 13 prepared by the Statistical reviewer, "black women had almost twice treatment improvement of Diclegis over placebo than that of white women."

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

As previously noted, the majority of subjects in Study DIC-301 experiencing symptoms of NVP required more than 28 tablets (minimum of 2 per night for 14 days) of study medication (67.9%, 89 of 131 Diclegis-treated subjects and 64.8%, 81 of 125 placebo-treated subjects). Based on individual response to study medication and a persistent PUQE score > 3, subjects could take 1 additional tablet in the morning and 1 additional tablet in the mid-afternoon, if needed, to control symptoms throughout the day.

Overall, sixty-four (64) of Diclegis-treated subjects (48.9%) and 41 of placebo-treated subjects (32.8%) requested to continue study medication (p=0.009) at the completion of Study DIC-301.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No discussions of persistence of efficacy and/or tolerance effects are presented in the NDA application.

6.1.10 Additional Efficacy Issues/Analyses

Per the application, the PUQE score based on 1) subjects with complete data via LOCF and 2) per protocol subjects were similarly performed separately for sensitivity purposes to examine the impact of missing data and data imputation. Table 14 shows the analysis for subjects with complete data presented in the application. Table 15 shows the PP analysis presented in the application.

Table 14: Sensitivity Analysis: Change from Baseline to Day 15 (± 1 day) in PUQE Score, Subjects with Complete Data via LOCF

Data/Category Subjects with Complete Data via LOCF	Statistics	Diclegis N = 131	Placebo N = 125
Baseline	N Mean ± SD Median Min, Max	101 9.0 ± 2.1 9.0 6, 15	75 8.7 ± 2.1 8.0 6, 15
Day 15 (± 1 day)	N Mean ± SD Median Min, Max	101 3.9 ± 1.6 3.0 3, 10	75 4.2 ± 1.7 4.0 3, 10
Change from baseline	N Mean ± SD Median Min, Max	101 -5.1 ± 2.5 -5.0 -11. 2	75 -4.5 ± 2.5 -4.0 -11, 1
P-value for Comparison	-	0.184[a]	-

Source: Adapted from NDA 21876, Clinical Study Report, Table 14.4.1.2.
a. P-values for treatment comparison (Diclegis vs. Placebo) from rank-based analysis of variance stratified by center.
Definitions: LOCF = last observation carried forward, SD = standard deviation, Min = minimum, max = maximum.

Table 15: Sensitivity Analysis: Change from Baseline to Day 15 (± 1 day) in PUQE Score, Per Protocol Subjects

Data/Category Per Protocol Subjects	Statistics	Diclegis N = 131	Placebo N = 125
Baseline	N Mean ± SD Median Min, Max	103 9.1 ± 2.1 9.0 6, 15	79 8.8 ± 2.1 8.0 6, 15
Day 15 (± 1 day)	N Mean ± SD Median Min, Max	103 3.8 ± 1.5 3.0 3, 10	75 4.2 ± 1.7 3.0 3, 10

Change from baseline	N Mean ± SD Median Min, Max	103 -5.3 ± 2.4 -5.0 -11. 2	75 -4.6 ± 2.4 -5.0 -11, 1
P-value for Comparison	-	0.069[a]	-

Source: Adapted from NDA 21876, Clinical Study Report, Table 14.4.1.2.
a. P-values for treatment comparison (Diclegis vs. Placebo) from rank-based analysis of variance stratified by center.
Definitions: LOCF = last observation carried forward, SD = standard deviation, Min = minimum, max = maximum.

Medical Officer's Comments:

Neither of the differences shown in Table 14 and Table 15 were statistically significant.

The Statistical reviewer also prepared sensitivity analyses providing the point estimate of the treatment difference between Diclegis and placebo and its 95% CI for the PUQE score and its 3 components for the complete data population, PP population and the completed study population. See the next two tables.

Table 16: Sensitivity Analysis: Change from Baseline to Day 15 (± 1 day) in PUQE Score

Population	Diclectin		Placebo		Diclectin vs. Placebo	
	n	Change from Baseline	n	Change from Baseline	Diff. (95% C.I.)	p-value
Per Protocol	103	-5.13	79	-4.64	-0.49 (-0.96,-0.01)	0.044
Complete Data	101	-4.93	75	-4.57	-0.36 (-0.86, 0.13)	0.148

Source: Statistical Reviewer's Analyses of NDA 21876, Table 8, page 12.
Definition: CI = confidence interval.

Table 17: FDA Sensitivity analyses: Change from Baseline to Day 15 (± 1 day) in PUQE Score and its Three Individual Components (Completed Study Population)

Population	Diclegis (n=112)	Placebo (n=91)	Diclegis vs. Placebo	
	Change from Baseline	Change from Baseline	Diff. (95% C.I.)	p-value
PUQE Score	-5.06	-4.72	-0.34 (-0.79, 0.11)	0.140
Hours of Nausea	-2.53	-2.47	-0.06 (-0.32, 0.20)	0.637
Number of Vomited	-1.03	-0.95	-0.08 (-0.19, 0.03)	0.156
Number of Retching	-1.49	-1.31	-0.18 (-0.35,-0.01)	0.035

Source: Statistical Review of NDA 21876, Table 7, page 12.
Definition: CI = confidence interval.

The results in Table 16 shows that only the PP population demonstrated a statistically significant treatment improvement of 0.49 out of a total 15 score (p=0.044).

The results in Table 17 shows that there was no treatment difference in the PUQE score and only one of the individual components, number of retching episodes, had a statistically significant improvement of 0.18 out of a total 5 score (p=0.035).

At the statistician request, the Applicant also provided a sensitivity analysis using a mixed model repeated measures (MMRM) model (using daily measure from day 1 to day 14 without imputation) to explore the sensitivity of imputation for missing values. This information was received December 5, 2012 and confirmed by the statistical reviewer. See Table 18.

Table 18: Mixed Model Repeated Measures (MMRM) Model[a]

Mixed Model for Repeated Measurement		
	P-value No Interaction Term	P-value Interaction Term (Treatment * Visit
Primary: PUQE Score	0.0003	0.0002**
Number of Hours of Nausea	0.0069	0.0074
Number of Times Vomiting	0.0014	0.0008**
Number of retching Episodes	0.0029	0.0024**

Source: Adapted from Applicant's response to information request received on December 5, 2012, response to question no. 3.

** Treatment and visit interaction is significant at level of 0.05.

a. Mixed model was applied with score as the response variable, treatment visit and baseline score as the independent variables.

Medical Officer's Comments:

The results for the MMRM sensitivity analysis show a significant treatment improvement in the PUQE score and for all 3 of its individual components. See the Statistical Review for more discussion regarding the results of the mixed model repeat measure analysis.

Medical Officer's Efficacy Summary Comments:

This reviewer recommends approval of Diclegis (10 mg doxylamine and 10 mg pyridoxine) delayed release oral tablets, taken as follows: 2 tablets at bedtime, 1 additional tablet taken in the morning, if needed, and 1 additional tablet taken mid-afternoon, if needed, for the treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management.

The data presented in the application for the single, placebo-controlled 15-day clinical trial supports the approval of Diclegis. A statistically significant difference between

Diclegis versus placebo was demonstrated (p=0.006). The analysis results confirmed a treatment improvement of -0.73 (95% CI, -1.25, -0.22) in pregnant women with NVP in the ITT-E population via LOCF.

The result of the analysis of the primary endpoint (mean change in the PUQE score from Baseline to Day 15) was supported by the analysis of the Global Assessment of Well-Being, one of the secondary efficacy endpoints. The mean change in the Global Assessment of Well-Being score from Baseline to Day 15 was statistically significantly higher in the Diclegis group than in the placebo group (p=0.005).

At the end of the 15-day clinical trial, 48.9% of subjects receiving Diclegis requested to continue on the study drug, as compared with 32.8% of placebo subjects indicating to this reviewer that the Diclegis treatment effect was clinically meaningful to the women in the Diclegis treatment group.

The 1975 FDA Review of the "8-way" study confirms that doxylamine alone and the combination of doxylamine and pyridoxine were effective in the control of nausea and vomiting of pregnancy. The FDA approved the combination of 10 mg doxylamine and 10 mg pyridoxine on November 4, 1976 for the treatment of "nausea and vomiting of pregnancy which are unresponsive to conservative measures such as ---."

In 1999, the Agency determined that Bendectin® was not "withdrawn from sale for reasons of safety or effectiveness" (Federal Register Notice, August 9, 1999).

7 Review of Safety

7.1 Methods

In the NDA application, data supporting the safety of Diclegis are derived from several sources including:

1. Data from the Clinical Study Report for the 15-day Phase 3 Study DIC-301.
2. Data from the 120-Day Safety Update received on October 5, 2012.
3. Data presented in the Summary of Clinical Safety for the 4 Phase 1 studies and Phase 3 Study DIC-301.
4. The Agency's August 9, 1999 determination of safety of the Reference Listed Drug, Bendectin® (10 mg doxylamine succinate and 10 mg pyridoxine HCL).
5. Safety data provided for Diclectin® (10 mg doxylamine succinate and 10 mg pyridoxine HCL) manufactured by Duchesnay Inc. in Canada.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Diclegis clinical development program consists of 5 studies which provided safety information:

- Study 02163; Phase 1 bioavailability study
- Study 02191; Phase 1 bioavailability study
- Study 70294; Phase 1 bioavailability study
- Study 70381; Phase 1 pharmacokinetic study
- Study DIC-301; Phase 3 safety and efficacy study

These 5 studies ranged from a single daily dose to 18 days of multiple dosing, and evaluated a single daily dose of 10 mg doxylamine/10 mg pyridoxine, single daily dose of 20 mg doxylamine/20 mg pyridoxine, and multiple doses of 20 mg doxylamine/20 mg pyridoxine up to multiple daily doses of 40 mg doxylamine/40 mg pyridoxine. See Table 19 for a summary of clinical studies.

Table 19: Summary of Clinical Studies Providing Safety Information

Study Identifier Type of Study	Study Design Study Objectives	Number of Subjects Route of Administration and Regimen	Treatment Duration
Study 70294 Bioavailability	Randomized, single-dose, crossover study separated by 27 days Effect of food on the bioavailability of doxylamine/pyridoxine under fasting and fed conditions	42 healthy adult females Oral dose 2 x 10 mg doxylamine/10 mg pyridoxine	A single oral dose was administered in each study period. The treatment phases were separated by a washout period of 27 days.
Study 02163 Bioavailability	Randomized, 2-way crossover, relative bioavailability To compare the rate and extent of absorption of delayed release doxylamine/pyridoxine tablet to oral solution under fasting conditions	22 healthy adult females Test product: oral 2 single doses of 10 mg doxylamine/10 mg pyridoxine Reference product: reconstituted powder	Each dose separated by a washout period of 28 days
Study 02191 Bioavailability	Randomized, 2-way crossover, relative bioavailability To assess the effect of food on the bioavailability of doxylamine/pyridoxine	22 healthy adult females Test product: oral 2 single doses of 10 mg doxylamine/10 mg pyridoxine	Each dose separated by a washout period of 28 days

	under fed and fasting conditions		
Study 70381 Pharmacokinetic	Single and multiple dose crossover Single and multiple dose safety and pharmacokinetic study in healthy nonpregnant female subjects	18 healthy adult females Oral single dose of 2 x 10 mg doxylamine/10 mg pyridoxine at 22:00 hours on Day 1 Oral multiple doses of a single 10 mg doxylamine/10 mg pyridoxine tablet at 9:00 hours and 16:00 hours and 2 x 10 mg/10 mg at 22:00 hours on Days 3 to 18	18 days
Study DIC-301 Safety and efficacy	Double-blind, randomized, placebo-controlled	203 completed pregnant subjects at least 18 years of age, with a gestational age of 4 to 14 weeks with NVP, a PUQE score of $\geq$ 6, and not responsive to conservative management	Study had a 15-day period consisting of 14 dosing days

Source: Adapted from NDA 21876, Tabular Listing of Clinical Studies, Table 5.2-1.

7.1.2 Categorization of Adverse Events

An AE was defined as any untoward medical occurrence, whether or not related to the study product, experienced by a subject on or after Day 1 (first dose administered) through Day 15 or the Early Termination Visit. For subjects who continued to receive medication for compassionate use, treatment-emergent adverse events (TEAEs) were collected for the 30 days following compassionate dispensation of the study drug.

The severity of the AE was assessed according to the following guidelines:

Mild: not limiting usual activities
Moderate: some limitations of usual activities
Severe: causing inability to perform usual activities

The investigator made a determination of the relationship of the AE to the study drug using the following guidelines:

Not Related: An AE that did not follow a reasonable temporal sequence from administration of the drug and that could be reasonably explained by other

factors, including underlying disease, complications, concomitant drugs, or concurrent treatment.

Unlikely: An AE that followed a reasonable temporal sequence from administration of the drug, but there was not a reasonable causal relationship between the administration of the drug and the AE.

Possible: An AE that followed a reasonable temporal sequence from the administration of the drug (including the course after withdrawal of the drug) and that could not be excluded as being possibly caused by the drug (e.g., existence of similar reports attributed to the suspected drug and/or its analogues; reactions attributable to the pharmacological effect of the drug), although other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment were presumable.

Probable: An AE that followed a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug) and that could be excluded as being possibly caused by other factors, such as underlying disease, complications, concomitant drugs, or concurrent treatment.

Definite: An AE that followed a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug), or followed a known or hypothesized cause effect relationship.

All AEs collected were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 10.0 or higher), classified by system organ class (SOC) and preferred term (PT).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

A Summary of Clinical Safety (SCS) is included in the application. The SCS provided information on the 5 above mentioned studies.

7.2 Adequacy of Safety Assessments

The frequency and severity of all adverse events were collected from subject diaries, visits, and phone call interviews and tabulated by treatment group, system organ class, preferred term, severity, and relationship to study drug. The relationship of adverse events to plasma/whole blood drug concentrations were also evaluated. In addition, laboratory tests, an obstetric ultrasound, and physical examination including vital signs were conducted.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A summary of the overall extent of exposure in the Diclegis clinical development program is shown in Table 20.

Table 20: Overall Extent of Exposure in the Diclegis Clinical Development Program

Study	Study Population	N	Daily Dose of Study Medication[a]	Duration of Use
Study 02163	Healthy, non-pregnant premenopausal women 18 to 45 years of age	22 randomized 18 completers	20/20	2 days with doses separated by 28 days
Study 02191	Healthy, non-pregnant premenopausal women 18 to 45 years of age	22 randomized 22 completers	20/20	2 days with doses separated by 28 days
Study 70294	Healthy, non-pregnant premenopausal women 18 to 45 years of age	44 randomized 42 completers	20/20	2 days with doses separated by 27days
Study 70381	Healthy, non-pregnant premenopausal women 18 to 45 years of age	18 randomized 18 completers	20/20 (2 days) 40/40 (16 days)	18 days
Study DIC-301	Pregnant women at least 18 years of age, gestational age 7 to 14 weeks	280 randomized 256 ITT-efficacy 261 ITT-safety	20/20 (minimum) 40/40 (maximum)	14 days

Source: Adapted from NDA 21876, Clinical Overview, Table 2.5-9, page 31 of 61.
a. Daily dose of mg of doxylamine succinate/mg pyridoxine hydrochloride.

The demographics for the 5 Diclegis clinical studies are summarized in Table 21.

Table 21: Summary of Diclegis Study Demographics

Category - Statistic	Study 02163 Safety Population N=22	Study 02191 Safety Population N=22	Study 70294 Safety Population N=44	Study 70381 Safety Population N=18	Study DIC-301 Safety Population N=132
Age (years) - Mean ± SD - Range	 29 ± 8 18 – 42	 32 ± 8 19 – 44	 30 ± 7 19 – 45	 33 ± 9 20 – 45	 26 ± 6 18 – 45
Race, N (%)					

- White	18 (81.8%)	19 (86.4%)	43 (97.7%)	18 (100%)	80 (60.2%)
- Black	1 (4.5%)	1 (4.5%)	1 (2.3%)	0	50 (37.6%)
- Asian	0	0	0	0	2 (1.5%)
- Other	3 (13.6%)	2 (9.1%)	0	0	1 (0.8%)
Weight					
- Mean ± SD	61.8 ± 8.3	61.6 ± 6.9	64.3 ± 7.9	66.4 ± 8.9	74.4 ± 22.4
- Range	47.9 – 76.4	51.3 – 73.2	50.0 – 81.0	53.5 – 83.6	40.6, 164.4
BMI (kg/m^2)					
- Mean ± SD	23.1 ± 2.6	23.0 ± 2.1	24.3 ± 2.7	24.9 ± 2.6	28.9 ± 7.6
- Range	19.1 – 28.1	20.1 – 28.4	19.5 – 29.6	20.1 – 29.4	16.7 – 53.2

Source: Adapted from NDA 21876, Summary of Clinical Safety, Table 2.7.4-2, page 7 of 44.

Medical Officer's Comments:

The notable difference across the 5 total studies conducted during the Diclegis development program include: 1) Phase 3 Study DIC-301 has a reasonable representation of a minority population (37.6% black), and 2) the weight and mean BMI were higher in Study DIC-301, probably due to the presence of the pregnancy.

The demographic and baseline characteristic for the single Phase 3 Study DIC-301 are shown in Table 4 on page 50 of this review

Medical Officer's Comments:

As shown in Table 4, the demographic characteristics of the study population in Study DIC-301 were similar between both treatment groups. Based on the information provided in Table 4, pregnant study participants waited approximately 4 weeks after the start of NVP to seek treatment. Study participants presented with approximately the same level of NVP severity at baseline (mean (SD) of 9.0 ± 2.1 for Diclegis-treated subjects and 8.8 ± 2.1 for placebo-treated subjects out of a possible 15 points).

7.2.2 Explorations for Dose Response

No exploration of dose response was included in the application.

7.2.3 Special Animal and/or In Vitro Testing

See the Pharmacology/Toxicology Review for a full discussion of special animal and/or *in vitro* testing in the Diclegis development program.

7.2.4 Routine Clinical Testing

The clinical evaluations conducted in Study DIC-301 met the recommended routine clinical standard for testing healthy pregnant women 18 to 45 years of age. See a description of the safety assessment, including the laboratory assessments, completed in Study DIC-301 on page 41 of this review.

7.2.5 Metabolic, Clearance, and Interaction Workup

No outstanding biopharmaceutical issues have been identified.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

No combination product containing 10 mg doxylamine and 10 mg pyridoxine is approved in the U.S. Diclectin® (10 mg doxylamine succinate and 10 mg pyridoxine HCL) delayed release tablet is approved for use in Canada and is "indicated in cases of nausea and vomiting of pregnancy."

The Canadian Monograph for Diclectin® (Date of Revision: April 30, 2009) indicated the following:

- "The most common adverse reaction associated with doxylamine succinate is drowsiness. Other adverse reactions associated with doxylamine succinate may include: vertigo, nervousness, epigastric pain, headache, palpitations, diarrhea, disorientation, irritability, convulsions, urinary retention or insomnia."

- "Pyridoxine is a vitamin that is generally recognized as having no adverse effects."

7.3 Major Safety Results

7.3.1 Deaths

No study subject deaths occurred in any of the five clinical trials conducted during the Diclegis development program. Fetal deaths in Study DIC-301 are described in Subsection 7.3.4 Significant Adverse Events in this review.

The 120-Day Safety Update Report, received on October 5, 2013, indicated "there are no new data to report" for the Diclegis development program.

7.3.2 Nonfatal Serious Adverse Events

No serious adverse events (SAEs) were reported in Phase 1 Studies 02163, 02191, 70294, and 70381.

In Study DIC-301, serious adverse events (SAEs) were collected from the time of the first dose until 30 days after the subject had either discontinued study medication or started on compassionate medication. As shown in Table 22, a total of 9 SAEs were reported for this study with 3.0% (4 of 133 Diclegis-treated subjects) in the Diclegis

treatment group, and 3.9% (5 of 128 placebo-treated subjects) in the placebo treatment group.

Table 22: Serious Treatment-Emergent Adverse Events in Phase 3 Study DIC-301, ITT-S Population

System Organ Class - Preferred Term	Diclegis (N = 133) n (%)	Placebo (N = 128) n (%)
Number of Subjects with at least one Serious TEAE	4 (3.0)	5 (3.9)
Hepatobiliary Disorders		
- Bile duct stone	0	1 (0.8)
Pregnancy, Peurperium and Perinatal Conditions		
- Abortion missed	1 (0.8)	1 (0.8)
- Abortion spontaneous	2 (1.5)	1 (0.8)
- Fetal disorder	0	1 (0.8)
- Intrauterine death	1 (0.8)	0
- Premature rupture of membrane	0	1 (0.8)

Source: Adapted from NDA 21876, Clinical Overview, Table 2.5-12, page 36 of 61, Summary of Clinical Safety, Table 2.7.4-8, page 20 of 44, and Clinical Study Report, Table 12.3, page 57 of 84.
Definitions: ITT-S = intent-to-treat – safety, TEAE = treatment-emergent adverse event.

Medical Officer's Comments:

Per the application, 8 of these 9 treatment-emergent serious adverse events (SAEs) were considered not related to the study medication and 1 of the 9 SAEs was considered unlikely related to study medication. Three (3) of the 9 listed treatment-emergent SAEs occurred during compassionate use of Diclegis following completion of Study DIC-301. Two (2) of the 9 listed treatment-emergent SAEs occurred within the 30-day window following the completion of Study DIC-301 in subjects who did not elect to continue compassionate use of Diclegis.

Table 22 shows similarity between the treatment groups in regards to pregnancy and perinatal outcomes/conditions, in particular missed/spontaneous abortions. More than 80% of spontaneous abortions are in the first 12 weeks of gestation, and at least half result from chromosomal anomalies. After the first trimester, both the spontaneous abortion rate and the incidence of chromosomal anomalies decrease.[9] For women in their childbearing years, the chances of having a spontaneous abortion can range from 10 to 25%. The reason for spontaneous abortion is varied, and most causes cannot be identified. Several factors may be involved including, but not limited to, maternal age, maternal health problems (for example, diabetes), maternal hormonal problems or infections, and lifestyle (for example, smoking, drug use, malnutrition, and excessive caffeine use).

9 Williams Obstetrics, 23rd Ed, Chapter 9 Abortion; McGraw-Hill; 2010:215-237.

7.3.3 Dropouts and/or Discontinuations

In Study DIC-301, there were 11 subjects that discontinued study drug due to an AE. Six (6) subjects were in the Diclegis treatment group (4.5%, 6 of 133 Diclegis-treated subjects), and 5 subjects were in the placebo treatment group (3.9%, 5 of 128 placebo-treated subjects).

Four (4) of the 11 events leading to early discontinuation (2 in the Diclegis treatment group [1 missed abortion and 1 spontaneous abortion] and 2 in the placebo treatment group [1 spontaneous abortion and 1 bile duct stone]) were considered serious treatment-emergent adverse events. These 4 cases are discussed below:

- Subject 11-001; Diclegis treatment group; 25 years of age; missed abortion:
  Screening ultrasound = 11 weeks gestation
  Medical/obstetrical history = recurrent pyelonephritis; previous miscarriage, previous elective cesarean delivery; no previous NVP
  First dose of study medication = 11 weeks gestation (March 18, 2008)
  Study drug daily use = 3 tablets
  Early termination date = March 27, 2008; refused End-of-Study procedures
  Missed abortion on (b) (6) = D&C performed; recovered; Investigator assessed event as severe and unlikely related to study drug.
- Subject 11-053; Diclegis treatment group; 24 years of age; spontaneous abortion:
  Screening ultrasound = 10 weeks gestation
  Medical/Obstetrical history = 4 spontaneous vaginal deliveries with NVP in each
  First dose of study medication = 10 weeks gestation (May 5, 2009)
  Study drug daily dose = 4 tablets
  Experienced vaginal bleeding = May 13, 2009
  Emergency room visit = placed on bed rest
  Hospitalized = (b) (6) spontaneous abortion; recovered with sequelae; last dose of study drug May 17, 2009
  Completed early termination procedures = May 20, 2009; Investigator assessed both events (vaginal hemorrhage and spontaneous abortion) as not related to study drug.
- Subject 11-047; placebo treatment group; 31 years of age; spontaneous abortion:
  Screening ultrasound = 8 weeks gestation
  Medical/Obstetrical history = 2 spontaneous vaginal deliveries with NVP in each
  First dose of study medication = 8 weeks gestation (March 26, 2009)
  Study drug daily dose = 4 tablets
  Vaginal bleeding = March 27, 2009
  Hospitalized = (b) (6) spontaneous abortion; recovered
  Early termination = March 29, 2009; Investigator assessed events as not related to study drug
- Subject 20-007; placebo treatment group; 32 years of age; bile duct stone:
  Screening ultrasound = 9 weeks gestation

Medical/Obstetrical history = cholecystectomy and recreational drug use, obstetric history of abortion, miscarriage, and 2 spontaneous vaginal deliveries with NVP in each
First dose of study medication = February 28, 2008 (only dose taken)
Hospitalization on (b) (6) = bile duct stone; treated; recovered
Early termination = March 4, 2008; Investigator assessed the event as severe and not related to study drug.

Medical Officer's Comments:

This reviewer concurs that the 4 subjects discussed above experienced serious adverse events that led to their discontinuation from Study DIC-301. As noted previously spontaneous abortion (also called miscarriage) is the most common type of pregnancy loss. This reviewer concurs with the Investigator assessment of causality in the 4 cases discussed above.

The 7 remaining events leading to study discontinuation (4 in the Diclegis treatment group and 3 in the placebo treatment group) were considered non-serious treatment-emergent adverse events in the application:

- Subject 10-012; Diclegis treatment group; 28 years of age; somnolence:
  Screening ultrasound = 7 weeks gestation
  Medical/Obstetrical History = Bell's palsy and ventricular septal defect; previous obstetrical history of vaginal abortion, 2 spontaneous miscarriages, and 2 spontaneous vaginal deliveries with NVP
  First dose of study medication = April 7, 2008 (only dose taken)
  Somnolence = April 8, 2008
  Early termination = April 9, 2008; recovered from event; Investigator assessed the event as mild and definitely related to study drug.
- Subject 10-015; Diclegis treatment group; 19 year of age; syncope:
  Screening ultrasound = 10 weeks gestation
  Medical/Obstetrical history = intermittent headaches; allergy to penicillin; previous emergency cesarean section, miscarriage, and abortion with NVP
  First dose of study medication = April 18, 2008
  Syncope = April 23, 2008
  Early termination = April 23, 2008; recovered; Investigator assessed the event as mild and possibly related to study drug.
- Subject 12-025; Diclegis treatment group; 22 years of age; somnolence:
  Screening ultrasound = 10 weeks gestation
  Medical/Obstetrical history = migraine headaches, gallbladder surgery, hypertension in previous pregnancy; obstetric history of 3 spontaneous vaginal deliveries with NVP in each
  First dose of study medication = October 21, 2008

Completed study = November 3, 2008; started compassionate use on November 4, 2008
Somnolence = November 10, 2008; discontinued compassionate study drug; recovered; Investigator assessed event as mild and possibly related to study drug.

- Subject 31-024; Diclegis treatment group; 32 years of age; dizziness:
  Screening ultrasound = 7 weeks gestation
  Medical/Obstetrical history = no previous history
  First dose of study medication = December 12, 2008 (only dose taken)
  Dizziness = December 12, 2008
  Early Termination = December 12, 2008; no treatment; Investigator assessed event as probably related to study drug
- Subject 10-036, placebo treatment group; 23 years of age; dyspepsia/intermittent headaches
  Screening ultrasound = 10 weeks gestation
  Medical/Obstetrical history = asthma; 3 spontaneous vaginal deliveries with NVP in each
  First dose of study medication = August 14, 2008
  Dyspepsia and intermittent headaches = August 17, 2008
  Early termination = August 18, 2008; recovered; Investigator assessed both events (dyspepsia and headaches) as mild and possibly related to study drug.
- Subject 12-030; placebo treatment group; 32 years of age; somnolence:
  Screening ultrasound = 8 weeks gestation
  Medical/Obstetrical history = back pain; previous emergency cesarean section and previous elective cesarean section with NVP in each
  First dose of study medication = November 11, 2008
  Somnolence = November 12, 2008
  Early termination = November 19, 2008; recovered; Investigator assessed event as mild and possibly related to study drug.
- Subject 12-035; placebo treatment group; 21 years of age; abdominal pain:
  Screening ultrasound = 8 weeks gestation
  Medical/Obstetrical history = spontaneous vaginal delivery with NVP
  First dose of study medication = January 16, 2009
  Study drug daily dose = 3 tablets
  Abdominal pain = January 22, 2009 to February 10, 2009
  Early termination = January 22, 2009; required no treatment; Investigator assessed event as mild and possibly related to study drug.

Medical Officer's Comments:

This reviewer concurs that these 7 subjects did not experience a serious adverse events in Study DIC-301. This reviewer also concurs with the Investigator's assessment that these cases were either definitely (1 case), probable (1 case), and possible related (5 cases) to study medication (4 subjects received Diclegis and 3

subjects received placebo) with Subject 10-036, in the placebo-treatment group, the possible exception (dyspepsia/intermittent headaches).

Somnolence, dizziness, syncope, and abdominal pain are reported side effects, among other reported side effects, with the use of antihistamines such as doxylamine. Two Diclegis-treated subjects and 1 placebo-treated subject discontinued Study DIC-301 due to somnolence.

7.3.4 Significant Adverse Events

The following significant adverse events were reported in Phase 3 Study DIC-301 that occurred while on compassionate use of Diclegis following completion of Study DIC-301:

- Subject 10-002; Diclegis treatment group during Study DIC-301; 32 years of age: intra-uterine death:
  Screening ultrasound = 6 weeks gestation
  Medical history = gunshot wound with removal of part of the pancreas and splenectomy; obstetric history of multiple spontaneous vaginal deliveries; no previous NVP
  First dose of study medication = 7 weeks gestation (February 22, 2008)
  Study drug daily use = 3 tablets
  Completed study = March 5, 2006 and continued compassionate Diclegis use
  Hospitalization = (b) (6) intra-uterine death; determined to be 9.6 weeks gestation with possible cystic hygroma; dilation and curettage (D&C) performed; recovered; Investigator assessed the event as severe and not related to study drug.
- Subject 11-030; Diclegis treatment group during Study DIC-301; 36 years of age; spontaneous abortion:
  Screening ultrasound = 8 weeks gestation
  Medical history = atypical depressive disorder; spontaneous vaginal delivery with NVP
  First dose of study medication = 9 weeks gestation (November 11, 2008)
  Study drug daily dose = 4 tablets
  Completed study = November 23, 2008 and continued compassionate Diclegis use
  Vaginal bleeding = November 24, 2008
  Hospitalized = (b) (6) spontaneous abortion; hospitalized for observation; Investigator assessed both events (vaginal hemorrhage and spontaneous abortion) as not related to study drug
- Subject 12-033; placebo treatment group during Study DIC-301; 19 years of age; missed abortion:
  Screening ultrasound = 8 weeks gestation
  Medical history = right upper quadrant abdominal pain, no previous obstetrical history
  First dose of study medication = 8 weeks gestation (December 4, 2008)

Study drug daily dose = 4 tablets
Completed study = December 18, 2008 and continued compassionate Diclegis use
Missed abortion = (b) (6); treatment with single dose misoprostol; recovered; Investigator assessed event as severe and not related to study drug

The following 2 subjects did not continue compassionate Diclegis use after completion of Study DIC-301, but reported adverse events within the 30-day window after completion of the study:

- Subject 30-005; placebo treatment group during Study DIC-301; 18 years of age; premature rupture of membranes:
  Screening ultrasound = 13 weeks gestation
  Medical history = vaginal bleeding with present pregnancy; no previous obstetric history
  First dose of study medication = 13 week gestation (May 12, 2008)
  Study drug daily dose = 4 tablets
  Completed study = May 28, 2008; did not continue on compassionate Diclegis use; unable to contact for 30 day follow-up phone call
  Reported SAE = June 6, 2008 of premature of membranes
  Hospitalization = (b) (6) single dose of misoprostol PO and intravaginally to induce labor; abortion; Investigator assessed event as not related to study drug; recovered; completed the study
- Subject 31-033; placebo treatment group during Study DIC-301; 24 years of age; fetal disorder:
  Screening ultrasound = 8 weeks gestation; no abnormal clinically significant findings
  Medical history = no previous medical or obstetrical history
  First dose of study medication = 8 weeks gestation (May 18, 2009)
  Study drug daily dose = 4 tablets
  Vaginal spotting = May 26, 2009 to May 28, 2009
  Completed study = June 1, 2009; did not continue compassionate Diclegis use
  30-day phone follow-up call = fetal disorder diagnosed on June 25, 200 (fetal echocardiogram showed ectopia cordis; ultrasound showed gastroschisis); underwent D&C; recovered; Investigator assessed event as severe and not related to study drug.

No significant adverse events were reported in Studies 02163, 02191, 70294, and 70381.

Medical Officer's Comments:

The occurrence of spontaneous abortion in early pregnancy has previously been discussed in this review.

7.3.5 Submission Specific Primary Safety Concerns

Use of Diclegis during Lactation:

Per the proposed Diclegis labeling submitted in the application and re-submitted on February 22, 2013, "The molecular weight of doxylamine succinate is low enough that passage into breast milk should be expected. (b) (4)

Pyridoxine hydrochloride is excreted into breast milk, (b) (4) These statements are supported by references in the published literature. Hale (2010) cautions against the use of doxylamine in premature neonates with apnea in particular, although the levels of doxylamine in human breast milk are not known. In addition, Hale (2010) reports that pyridoxine readily transfers into breast milk and that B_6 levels correlate closely with maternal intake.

Medical Officer's Comments:

The information that the "molecular weight of doxylamine is low enough that passage into breast milk should be expected" should be included in the Diclegis labeling. The additional referenced health information regarding the (b) (4) *should also be considered for inclusion in the labeling for Diclegis.*

Overdose of 10 mg Doxylamine and 10 mg Pyridoxine:

Diclegis is a delayed release tablet; therefore signs and symptoms of intoxication may not be apparent immediately. Per the Diclegis labeling submitted in the application and re-submitted on February 22, 2013, "Signs and symptoms of (b) (4) may include restlessness, dryness of mouth, dilated pupils, sleepiness, vertigo, mental confusion, and tachycardia. If treatment is needed, it consists of gastric lavage or activated charcoal, whole bowel irrigation and a symptomatic treatment. For additional information about overdose treatment, call a poison control center (1-800-222-12222)."

Per the application, "At toxic doses (2400 mg or 60 times the normal daily dose), doxylamine exhibits anticholinergic effects, including seizures, rhabdomyolysis, and death. A prospective study on doxylamine overdosage identified that 16 of 27 patients developed rhabdomyolysis and 3 of these 16 patients developed acute renal failure)."

Per the application, (b) (4) See Subsection 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound of this review for a discussion of a fatal case of doxylamine

alone overdose presented in the 120-Day Safety Update Report received on October 5, 2012. Per the application, the lethal dosage of doxylamine in humans is reported as 25-250 mg/kg body weight.

Medical Officer's Comments:

These reported signs and symptoms pertain to the doxylamine component of Diclegis. It is, therefore, appropriate to included the signs and symptoms of overdosage in labeling as well as the treatment procedures and specific measures that may be needed for support of vital functions.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Treatment-emergent adverse events (TEAEs) were defined as AEs experienced by the subjects that occurred on or after Day 1 (first dose administered) through Day 15 or the Early Termination Visit. For subjects who continued to receive medication for compassionate use after Day 15, TEAEs were collected for the 30 days following compassionate dispensation of the study drug.

The common adverse events reported in the 4 Phase 1 studies in the Diclegis development program are illustrated below by study:

- Study 02163: Headache (23.0%, 17 subjects)
  Nausea (16.2%, 12 subjects)
- Study 02191: Headache (11.8%, 6 subjects)
- Study 70294: Headache (13.6%, 6 subjects)
  Catheter site pain (13.6%, 6 subjects; used for blood sampling)
  Somnolence (11.4%, 5 subjects)
- Study 70381: Nausea (50%, 9 subjects)
  Headache (44%, 8 subjects)

Medical Officer's Comments:

As previously noted, the Phase 1 studies involved single and multiple doses, and included daily doses of 10 mg doxylamine/10 mg pyridoxine and 20 mg doxylamine/20 mg pyridoxine, and multiple doses up to 40 mg doxylamine/40 mg pyridine daily. The adverse events reported among the 4 Phase 1 studies are not unexpected adverse effects and are similar to the adverse events reported in the Phase 3 Study DIC-301.

The occurrence of catheter site pain in Phase 1 Study 70381 is also not unexpected, due to the placement of an indwelling catheter to facilitate blood collection.

Of the 261 ITT-S subjects in Study DIC-301, seventy-four (74) of the 133 Diclegis-treated subjects (55.6%) experienced at least 1 TEAE versus 66 (55.6%) of the 128 placebo-treated subjects. The most common adverse events in Study DIC-301 are shown in Table 23.

Table 23: Common Treatment-Emergent Adverse Events (≥ 2 %) in Study DIC-301

Adverse Event System Organ Class - Preferred Term	**Diclegis N=133 n (%)**	**Placebo N=128 n (%)**
Gastrointestinal Disorders	**23 (17.3)**	**22 (17.2)**
- Abdominal pain	5 (3.8)	8 (6.3)
- Abdominal pain upper	3 (2.3)	5 (3.9)
- Diarrhea	4 (3.0)	2 (1.6)
- Dry mouth	4 (3.0)	1 (0.8)
- Dyspepsia	5 (3.8)	2 (1.6)
- Nausea	2 (1.5)	3 (2.3)
General Disorder and Administration Site Cond.	**13 (9.8)**	**12 (9.4)**
- Fatigue	9 (6.8)	8 (6.3)
Infections and Infestations	**8 (6.0)**	**10 (7.8)**
- Nasopharyngitis	3 (2.3)	5 (3.9)
Musculoskeletal and Connective Tissue Disorders	**11 (8.3)**	**4 (3.1)**
- Back pain	7 (5.3)	4 (3.1)
- Pain in extremity	4 (3.0)	0 (0.0)
Nervous System Disorder	**42 (31.6)**	**37 (28.9)**
- Dizziness	8 (6.0)	8 (6.3)
- Headache	17 (12.8)	20 (15.6)
- Somnolence	19 (14.3)	15 (11.7)
Reproductive System and Breast Disorders	**8 (6.0)**	**6 (4.7)**
- Vaginal hemorrhage	5 (3.8)	3 (2.3)
Respiratory, Thoracic and Mediastinal Disorders	**6 (4.5)**	**3 (2.3)**
- Cough	3 (2.3)	1 (0.8)

Source: Adapted from NDA 21876, Clinical Study Report for Study DIC-301; Table 14.5.2 in 14.3 Safety Summary Tables and Figures, page 64 of 84.

Medical Officer's Comments:

The number of subjects experiencing adverse events, as shown in Table 23, is not significantly different between the two treatment groups.

In Study DIC-301, there were 2 severe TEAEs considered related to Diclegis including fatigue (possible) and fatigue/exhaustion (probable), and 1 severe TEAE considered related to placebo (headache, possible).

Study DIC-301 did not demonstrate any safety or tolerability concerns for Diclegis (2 tablets daily up to a maximum of 4 tablets daily) used to treat nausea and vomiting of pregnancy.

Common Adverse Events Reported with Bendectin®:

In the application, the Applicant provides a 1975 FDA Review of a randomized, double-blind, multi-center, placebo-controlled study of Bendectin® conducted in 2,308 women with NVP under NDA10598/ (b) (4) Doses of 10 mg doxylamine, 10 mg dicyclomine hydrochloride, and 10 mg of pyridoxine, alone or in various combinations, were compared with placebo over 7 days in an 8-way study design. Treatment groups included:

1) Bendectin® 1956 original formulation (10 mg doxylamine and 10 mg dicyclomine HCL and 10 mg pyridoxine)
2) 10 mg doxylamine and 10 mg pyridoxine
3) 10 mg dicyclomine HCL and 10 mg doxylamine
4) 10 mg doxylamine alone
5) 10 mg dicyclomine HCL and 10 mg pyridoxine
6) 10 mg pyridoxine alone
7) 10 mg dicyclomine HCL alone
8) Placebo

See page 55 of this review for a brief description of the study design of this “8-way” study.

Per the 1975 FDA Review of the study, “No serious adverse effects were reported for any of the medications (full summary in this volume). The incidence of reported adverse effects among the medication groups varied from 8.7% for doxylamine/pyridoxine (versus 11.2% in the placebo group) to 15.2% for doxylamine, with a mean of 12% for the total population. Drowsiness was an adverse effect relatable to one of the ingredients (doxylamine) of Bendectin. Patient groups taking medication which contained doxylamine had an incidence of drowsiness from 1.56% to 2.69% above placebo, whereas patients taking dicyclomine, pyridoxine, or a combination of dicyclomine/pyridoxine had an incidence of drowsiness of 1.42% or more below placebo. The incidence of drowsiness among placebo patients was 2.97%.” See the following illustration of the overall percent of subjects experiencing 1 or more adverse events in each of the 8 treatment groups.

Medication Group	% of Subjects
Bendectin	14.3
Doxylamine/pyridoxine	8.7
Dicyclomine HCL/doxylamine	13.4

Doxylamine alone	15.2
Dicyclomine HCL/pyridoxine	12.4
Pyridoxine alone	9.6
Dicyclomine HCL alone	10.7
Placebo	11.2
Total	12.0

The most common adverse events for the treatment and placebo groups, in this study, are listed in Table 24.

Table 24: Common Treatment-Emergent Adverse Events (≥ 1 %) in the 8-Way Bendectin® Clinical Study Conducted under NDA 10598

Adverse Event	**Bendectin[a] N=265 n (%)**	**Placebo N=269 n (%)**
Drowsiness	15 (5.7)	8 (3.0)
Dizziness	3 (1.1)	2 (0.7)
Fatigue or lethargy	2 (0.7)	3 (1.1)
Gastric irritation, heartburn, or indigestion	2 (0.7)	0 (0.0)
Headache	2 (0.7)	4 (1.5)

Source: Adapted from NDA 21786, Clinical Overview, Table 2.5-10, page 32 of 62; and the FDA 1975 Review, Tables A, page 48.

a. In the Bendectin® 1975 study review of NDA 10598/ (b) (4) the results are shown for a Decapryn/Pyridoxine combination, the same active ingredients of doxylamine/pyridoxine.

Medical Officer's Comments:

The TEAEs reported in the "8-way" 1975 study in Table 24 are similar to the TEAEs shown in Table 23 for Study DIC-301.

(b) (4)

The following adverse reactions are reported in labeling for Bendectin® that was retrieved for (b) (4) and dated July, 1982:

(b) (4)

Medical Officer's Comments:

(b) (4).

Common Adverse Events Reported for Diclectin® (10 mg Doxylamine and 10 mg Pyridoxine) Approved in Canada:

Post-marketing safety data for Diclectin® for the period February 1, 2012 to September 1, 2012 is included in the 120-Day Safety Update Report. During this reporting period, 18 spontaneous case reports (individuals) representing a total of 38 adverse drug reactions (ADRs) were collected by Duchesnay. Among the 18 case reports collected during this reference period, 2 were classified as serious and unexpected and the remaining 16 were non-serious cases (4 unexpected and 11 expected ADRs). Both of the reported serious cases involved drug ineffectiveness. The non-serious cases involved, but are not limited to, continued nausea and/or vomiting, seeing whole tablets in vomitus (2 cases), and increasing daily tablet intake to 7 tablets for relief (2 cases).

The 120-Day Safety Update Report, received on October 5, 2013, also includes information on two ongoing studies of Diclectin® being conducted in Canada. Study #0020010091, Part 2 is an extension of Part 1, an observational cohort design study of mother-child pairs to determine the effects of NVP and its treatment with Diclectin® on child neurodevelopment (45 children of mothers with NVP and Diclectin® use during pregnancy, 47 children of mothers with NVP and no Diclectin® use during pregnancy, and 29 children with mothers without NVP during pregnancy). In part 1, the investigators concluded that "NVP has an enhancing effect on later child outcome. Further, Diclectin® did not appear to adversely affect fetal brain development and can be used to control NVP when clinically indicated." Part 2 which began in November 2004 and is ongoing, involves women taking more than the recommended Diclectin® dose (instead of a total of 4 tablets [recommended dose] these women are taking 5-12 tablets per day). Per the 12-Day Safety Update Report, no ADRs have been reported between February 1, 2012 and September 1, 2012 in this study. In a 2001 publication, Atanackovic et al. reports that, "Despite a 2-fold greater mean maximal dose of Diclectin, women receiving the supradose did not report more prevalent adverse effects of Diclectin. In the supradose group, 32% (31/97) reported sleepiness, tiredness and/or drowsiness compared with 35% (42/122) among the standard dose recipients."[10] In addition, two pregnancies were diagnosed with major malformations (1 case each of anencephaly [terminated] and ventricular septal defect). Both occurred in the standard dose group.

Medical Officer's Comments:

Per the Aranackovic et al. (2001) publication, the finding of 2 cases of major malformations in the study population is consistent with rates of birth defects in the general population. This reviewer concurs. The background risk of major

10 Aranackovic G. Navioz Y, Moretti ME, Koren G. The safety of higher than standard dose of doxylamine-pyridoxine (Diclectin) for nausea and vomiting of pregnancy. J Clin Pharmacol 2001;41:842-845.

malformations for all pregnancies is approximately 1-3%. This is the risk of having a child with a birth defect when no drugs or chemicals are taken during pregnancy.

The primary objective of the second ongoing study (Study #1000007791) is to assess the effectiveness of pre-emptive Diclectin® treatment in women who have experienced severe NVP/hyperemesis gravidarum in their previous pregnancy, compared to women with a similar previous experience not receiving such pre-emptive intervention. No serious or non-serious AEs were reported to Duchesnay Inc. between February 1 2012 and September 1, 2012 for this study.

The adverse events reported for Diclectin® (10 mg doxylamine and 10 mg pyridoxine) approved in Canada since 1983 are discussed in Section 8 Postmarketing Experience of this review.

7.4.2 Laboratory Findings

Safety laboratory assessments included hematology, serum chemistry, and urinalysis were performed in Study DIC-301. See Table 3 of this review.

For each visit, the number of subjects with clinically significant assessments was summarized, and changes from baseline were assessed using shift tables including the following categories:

1. Shift: no change = (No → No, Yes → Yes);
2. Worsening = (No → Yes);
3. Improvement = (Yes → No)

In the 4 Phase 1 studies overall, the majority of post-dose results were within normal limits. The exceptions are listed below:

- Subject No. 12 in Study 02163 had a post-study hemoglobin of 109 g/L (normal range 120-160 g/L). This subject was lost to follow-up. A repeat test was not performed.
- Subject No.16 in Study 02163 had a post-study hemoglobin of 109 g/L. A repeat test performed 24 days later was 110 g/L. A repeat urinalysis yielded normal results.
- Subject No. 17 in Study 02191 had a post-study hemoglobin of 107 g/L. A repeat hemoglobin 36 days later was 120 g/L).
- Subject No. 22 in Study 70294 had a post-study hemoglobin of 109 g/L with a repeat of 106 g/L. She was referred to her family physician for follow-up. Each subject had approximately 446 mL of blood collected during Study 70294. No additional information is provided for this subject.

In Phase 3 Study DIC-301, there were no overall noteworthy differences between treatment groups in the shift from baseline during dosing for any of the blood chemistry

parameters, hematology laboratory values, or urinalysis laboratory values. The exceptions were:

- One Diclegis-treated subject (Subject 20-002) was reported to have a TEAE of decreased platelet count. This event was considered mild in severity and unlikely related to study drug.
- A shift from baseline was observed in ≥ 20% of subjects for hematocrit and hemoglobin in both treatment groups.
- A shift from baseline was observed in > 20% of subjects for urinary ketones and specific gravity in both treatment groups.

Medical Officer's Comments:

In the 4 Phase 1 studies and in Phase 3 Study DIC-301, no differences between treatment groups in the shifts from baseline during dosing for these laboratory assessments are considered to be clinically significant. No subjects discontinued due to shifts from baseline in any laboratory findings.

7.4.3 Vital Signs

In the 4 Phase 1 studies, the majority of final vital signs measurements were within normal limits. No clinically remarkable differences were noted in 3 of the 4 Phase 1 studies. In Study 70381, 6 subjects had reported blood pressure decreases and 4 subjects were reported to have an increase heart rate in the 18-day study. No subjects discontinued Study 70381.

No clinically remarkable differences in vital signs or physical examinations were observed in Study DIC-301.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not routinely performed in the Diclegis development program.

7.4.5 Special Safety Studies/Clinical Trials

Per the proposed labeling for Diclegis, (b) (4)

Per the proposed labeling for Diclegis, (b) (4)

(b) (4)

(b) (4)

In proposed Diclegis labeling, under Subsection 12.3 Pharmacokinetics, *Excretion,* the Applicant proposes this information, (b) (4)

Medical Officer's Comments:

See the Clinical Pharmacology Review for a full discussion of the use of Diclegis in specific populations, including populations with renal or hepatic impairment.

7.4.6 Immunogenicity

No human immunogenicity studies, data, or published literature regarding same were submitted in the NDA application.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No clear dose dependency for adverse events was observed in Phase 3 Study DIC-301.

7.5.2 Time Dependency for Adverse Events

Phase 3 Study DIC-301 was only a 15-day study.

7.5.3 Drug-Demographic Interactions

No drug-demographic interactions were reported in the NDA application.

The Statistical reviewer prepared a subgroup analysis of efficacy by race for Study DIC-301 (see Subsection 6.1.7 Subpopulations of this review). Based on the Statistical reviewer's analysis, black study participants had an almost 2-fold greater improvement in NVP over placebo than white study participants.

(b) (4)

7.5.4 Drug-Disease Interactions

The Clinical Study Report for Study DEC-301 indicates that drug-disease interactions were not investigated in Study DIC-301.

7.5.5 Drug-Drug Interactions

The Clinical Study Report for Study DEC-301 indicates that drug-drug interactions were not investigated in Study DIC-301. However, the application proposes to include the following contraindications in Diclegis labeling:

(b) (4)

Per the application, the proposed Diclegis labeling contraindications are taken from publications including: (b) (4)

The "theoretical" drug-drug interactions with doxylamine and pyridoxine, summarized in the following two tables, are included in the Diclectin® Product Monograph (b) (4) .

(b) (4)

(b) (4)

Medical Officer's Comments:

See the Clinical Pharmacology Review for a discussion of drug-drug interactions for doxylamine and pyridoxine validated by the published literature. See the Clinical Pharmacology Review for recommendations for drug-drug interaction inclusions in Diclegis labeling.

7.6 Additional Safety Evaluations

As previously noted in this review, Bendectin® has been the subject of many epidemiologic studies (case-control and cohort) and FDA reviews intended to determine whether or not Bendectin® is associated with teratogenicity. Overall, a review of the results of these studies leads to the conclusion that the existing data do not demonstrate an association between Bendectin® use and birth defects.

Per the Agency's Review of Bendectin® dated April 18, 1977:

> "A search of the DIVISION files for Bendectin shows Medical Officer's Review (7/9/68) wherein all defects reported between 1957 and 1968 are tabulated. A total of 39 birth defects are reported. Five of these are phocomelia. It was concluded that Bendectin was a "safe drug"."
>
> "No publications were found that proved Bendectin to be the cause of congenital malformations. In summary, no scientific evidence has been found that Bendectin may cause birth defects."

Medical Officer's Comments:

See Subsection 7.6.2 Human Reproduction and Pregnancy Data for a brief discussion of the published literature.

On August 9, 1999, FDA made a determination that Bendectin® was indeed "not withdrawn from sale for reasons of safety and effectiveness". Per the August 9, 1999 Federal Register Notice:

"The agency's review of the withdrawal of Bendectin from the market has considered the sponsor's explanation of the basis for the withdrawal of the product in 1983 and information available to the agency regarding safety and effectiveness concerns for Bendectin. As noted previously, the sponsor has consistently maintained that it withdrew Bendectin from the market for reasons other the safety and effectiveness. The agency has reviewed information submitted with the petitions, published studies, U.S. and foreign adverse event reports, and FDA records. The current evidence supports the conclusion that Bendectin was not withdrawn from the market for reasons of safety or effectiveness."

7.6.1 Human Carcinogenicity

The Pharmacology/Toxicology reviewer has included the following information in Diclegis labeling: "Two-year carcinogenicity studies in rats and mice have been conducted with doxylamine succinate. The results were of questionable significance in humans, and doxylamine succinate is not likely to have human carcinogenic potential."

7.6.2 Human Reproduction and Pregnancy Data

The Applicant provides two separate meta-analyses in the application in support of the safety of the combination of 10 mg doxylamine and 10 mg pyridoxine, with or without 10 mg dicyclomine HCl, given during the first trimester of pregnancy. McKeigue et al. (1994) conducted a meta-analysis of 16 cohort and 11 case-control studies published between 1963 and 1991. No increased risk for malformations was found in first trimester exposures to doxylamine and pyridoxine, with or without dicyclomine hydrochloride.[12]

A second meta-analysis, conducted by Einarson et al. (1988) incorporated 12 cohort and 5 case control studies published between 1963 and 1985. No statistically significant relationships were found between first trimester use of the combination doxylamine and pyridoxine, with or without dicyclomine HCl, and fetal abnormalities.[13]

12 McKeigue PM et al. Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies. Teratology. 1994;50:27-37.
13 Einarson TR et al. A method for meta-analysis of epidemiological studies. Drug Intell Clin Pharm. 1988; 22:8130824.

In addition, other published literature that report on the human reproductive and teratogenic effects of Bendectin® was available for review in the application. Brent (1995), in a publication which addresses the Bendectin® litigation ongoing at that time, reviewed the published literature including epidemiologic studies, animal studies, in vitro studies, basic science articles, review articles, meta-analyses, and case reports. His publication presents analyses of epidemiologic studies, secular trend analysis, animal studies, dose-response relationships, and biologic plausibility. The publication concludes that "therapeutic use of Bendectin has no measurable teratogenic effect."[14]

7.6.3 Pediatrics and Assessment of Effects on Growth

Per the application, The Motherisk Program at the Hospital for Sick Children has completed the first phase of a prospective observational blinded cohort study with control groups to assess the effect of in utero exposure to the recommended dose (up to 4 tablets a day) of Diclectin® on child neurodevelopment and to study the dose response effects of exposure in utero to recommended doses in regard to neurobehavioral performance of the exposed child. A total of 121 female subjects were included into phase 1 of the study after being recruited via the Motherisk NVP Helpline or Motherisk Home Line. Women and their children constituted the study and comparison groups in this project. Subjects were not assigned to treatment groups, but were asked to participate in the study and included in the study or comparison groups based on the NVP treatment prescribed by their physician. No serious adverse drug reactions were reported during the study. The study concludes that Diclectin® does not adversely affect fetal central nervous system (CNS) development.[15] Phase 2 of this study is currently ongoing to assess the effect of higher than standard (supra-therapeutic) doses of Diclectin® on child neurodevelopment.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

One fatal case of overdose of doxylamine alone is reported in the 120-Day Safety Update Report dated (b) (6). A 13 month old girl with no previous history of disease was prescribed an OTC drug (Sedaplus® Saft) containing 250 mg doxylamine/100 mL by her private doctor for teething problems. She was found lifeless the day after receiving 3.5 ml of the OTC product. An autopsy reported "aspiration of stomach contents" to be the cause of death.

Per the application, other fatalities have been reported from doxylamine overdose. These overdose cases are characterized by coma, grand mal seizure and cardiorespiratory arrest. In particular, children appear to be at high risk for

14 Brent RL. Bendectin: review of the medical literature of a comprehensively studied human nonteratogen and the most prevalent tortogen-litigen. Reprod Toxical. 1995 Jul-Aug:9(4):337-334.
15 Nulman I et al. Long-term Neurodevelopment of Children Exposed to Maternal Nausea and Vomiting of Pregnancy and Diclectin. J Pediatr. 2009.

cardiorespiratory arrest. "A toxic dose for children of more than 1.8 mg/kg has been reported." Koppel et al. (1987) reports, however, that there is "no correlation between the amount of doxylamine ingested, the doxylamine plasma level and clinical symptomatology."[16]

Per the application, two postmarketing overdose reports have been reported to the Canada Vigilance Program for products containing doxylamine. However, the dosage ingested and the blood concentrations of doxylamine were not reported. In the medical literature, the lethal dose of doxylamine in human is reported as 25-250 mg/kg body weight.[17]

The application does not include any information on (b) (4). The following information is provided in the Diclectin® Product Monograph, however, (b) (4) (b) (4) This information is also provided in the proposed Diclegis labeling.

Medical Officer's Comments:

Although the Applicant includes the above information regarding (b) (4) in the proposed Diclegis labeling, no information is provided in the application to suggest (b) (4) No specific (b) (4) information was provided in the protocol for Phase 3 Study DIC-301. No specific (b) (4) information is provided in the Diclectin® Product Monograph either.

7.7 Additional Submissions / Safety Issues

See Subsection 7.3.4 Significant Adverse Events and Subsection 7.3.5 Submission Specific Safety Concerns of this review.

8 Postmarket Experience

Postmarketing Experience with Bendectin® (10 mg Doxylamine Succinate/10 mg Pyridoxine Hydrochloride) Delayed Release Tablets:

16 Koppel c, Tenezer J, Ibe K. Poisoning with over the counter doxylamine preparations: an evaluation of 109 cases. Hum. Toxicol. 1987 6:355-359.
17 Bockholdt B, Klug E, Schneider V. Suicide through doxylamine poisoning. Forensic Sci Intl. 2001; 119:138-140.

T he Applicant provides the following information taken from an FDA statement on Bendectin®. There is no date stamp on the document, however (this reviewer estimates 1976/1977):

> "During the approximately 20 years that Bendectin has been marketed, an estimated (b) (4) pregnant women worldwide have received the drug or about (b) (4) per year. Since the U.S. distribution represents about (b) (4) of the total, an estimated (b) (4) U.S. women receive the drug annually based upon recent distribution figures." "If one utilizes an average U.S. figure of (b) (4) pregnant women, then the over the 20 years of marketing, (b) (4) pregnant women have received the drug in the U.S."
>
> "The FDA has in its file 86 cases of birth defects; the manufacturer has 130 cases (including the 86 cases in FDA files). This discrepancy is apparently due to literature reports which are coded into the manufacturer's files but not the FDA's. Many of the cases are from foreign countries. The defects range from the minor (e.g., bifid thumb, missing digits) to the moderate (e.g., cleft palate, club foot) to the more severe (e.g., limb reduction, major internal organ abnormalities, absent brain)."
>
> "Because of the extensive use of Bendectin during pregnancy, FDA has monitored closely the reports of birth defects, and has reviewed the published literature on controlled epidemiological studies of birth defects to determine whether Bendectin might be associated with an increased risk for such defects. There is no evidence of any risk due to Bendectin. In addition, Bendectin, its doxylamine component, and doxylamine plus pyridoxine components have been the subject of a large number of reproductive studies in rats and rabbits at doses as high as approximately 100 times the maximum human dose. There has been no evidence in these animal studies that Bendectin or its components cause birth defects."
>
> "In conclusion, it is not possible to state unequivocally that any drug is free of any possible risk either to a patient who receives the drug or to a child born of a mother who received the drug. The data on Bendectin are quite reassuring, however. If Bendectin is associated with any risk to an unborn child, the risk is so small that it cannot be detected by the large scale studies performed by Heinonen and associates; Milkovich and van der Berg; and Oakley."

Postmarketing Experience with Diclectin® (10 mg Doxylamine Succinate/10 mg Pyridoxine Hydrochloride) Delayed Release Tablets:

Diclectin® (10 mg doxylamine and 10 mg pyridoxine) tablets have been marketed in Canada since 1975 and specifically by Duchesnay since 1983. The Applicant provides 6 Diclectin® PSURs in the application that cover the period 1983 to January 31, 2012. Post-marketing safety data for Diclectin® for the period February 1, 2012 to September

1, 2012 is included in the 120-Day Safety Update Report (see Subsection 7.4.1 Common Adverse Events).

Based on the information available in the 6 PSURs, Diclectin® has been used by over an estimated (b) (4) women in Canada. Summaries of the adverse events reported during the postmarketing period from 1983 to January 31, 2012 are listed alphabetically below:

"Cardiac disorders: dyspnea, palpitation, tachycardia
Congenital, familial and genetic disorders: congenital anomalies*, tooth hypoplasia*
Ear and labyrinth disorders: ear discomfort, vertigo
Eye disorders: mydriasis, photophobia, vision blurred, visual acuity reduced, visual brightness
Gastrointestinal disorders: abdominal distension, abdominal pain, constipation, diarrhea, flatulence, hematemesis, nausea, tongue discoloration, vomiting
General disorders and administration site conditions: chest discomfort, death, developmental delay*, discomfort, drug withdrawal syndrome, drug withdrawal syndrome neonatal*, fatigue, feeling abnormal, foaming at mouth, irritability†, malaise, edema peripheral, pain
Infections and infestations: tonsillitis streptococcal
Immune system disorders: hypersensitivity
Injury, poisoning and procedural complications: overdose
Investigations: brachial pulse decreased, weight loss
Metabolism and nutrition disorders: hyperglycaemia, hypokalaemia
Musculoskeletal and connective tissue disorders: musculoskeletal pain, pain in extremity
Nervous system disorders: convulsions*, dizziness, headache, hypoesthesia, hypersomnia*, loss of consciousness, migraines, paresthesia, psychomotor hyperactivity, somnolence
Pregnancy, puerperium and perinatal conditions: abortion spontaneous, fetal distress syndrome*, fetal hypokinesia*, intra-uterine death*, jaundice neonatal*, premature baby*, premature labour, uterine contractions during pregnancy
Psychiatric disorders: anxiety, attention deficit/hyperactivity disorder*, depression, disorientation, impatience, insomnia, mood swings, nightmares
Renal and urinary disorders: dysuria, renal cyst*, urinary retention
Reproductive system and breast disorders: vaginal hemorrhage
Respiratory, thoracic and mediastinal disorders: hypoxia
Skin and subcutaneous tissue disorders: angioedema, erythema multiforme, hyperhidrosis, pruritus, rash, rash maculo-papular, skin discoloration
Social circumstances: mental disability*
Vascular disorders: hypotension, peripheral coldness

*with respect to fetus/child
†with respect to woman and child

Post-marketing safety data for Diclectin® for the period February 1, 2012 to September 1, 2012 is included in the 120-Day Safety Update Report. During this reporting period, 18 spontaneous case reports (individuals) representing a total of 38 adverse drug reactions (ADRs) were collected by Duchesnay. Among the 18 case reports collected during this reference period, 2 were classified as serious and unexpected and the remaining 16 were non-serious cases (4 unexpected and 11 expected ADRs). Both of the reported serious cases involved drug ineffectiveness. The non-serious cases involved continued nausea and/or vomiting, seeing whole tablets in vomitus (2 cases), and increasing daily tablet intake to 7 tablets for relief (2 cases).

The 6 PSURs submitted in the application were reviewed in their entirety. Of special interest to this reviewer are the reported cases in the following System Organ Class (SOC) of: 1) Congenital, Familial and Genetic Disorders, and 2) Pregnancy, Puerperium and Perinatal Conditions. In the 6 PSURs reviewed, a total of 15 cases occurred under the SOC of Congenital, Familial and Genetic Disorders, and a total of 8 cases occurred under the SOC Pregnancy, Puerperium and Perinatal Conditions.

The Diclectin® PSUR #4, which covers the reporting period February 1, 2009 to January 31, 2010, provides a cumulative summary of the SAEs for these two above mentioned SOCs for the period 1983 to January 31, 2010. The cumulative unexpected SAEs, shown below, are from spontaneous notifications to Duchesnay and Canada Vigilance (regulatory authority), and from the literature:

MedDRA Preferred Terms, Version 13.0	Duchesnay Inc.	Canada Vigilance	Literature
SOC: Congenital, Familial, and Genetic Disorders (Total=12)			
Anencephaly	0	0	1
Congenital anomaly	0	1	0
Congenital brain damage	0	1	0
Congenital foot malformation	0	1	0
Congenital hand malformation	0	1	0
Congenital joint malformation	0	1	0
Congenital osteodystrophy	0	1	0
Dysmorphism	0	1	0
Phalangeal agenesis	0	1	0
Polydactily	0	1	0
Tooth hypoplasia	0	1	0
Ventricular septal defect	0	0	1
SOC: Pregnancy, Puerperium and Perinatal Conditions (Total=6)			
Abortion spontaneous	0	1	0
Intrauterine death	2	1	0

Jaundice neonatal	0	1	0
Premature baby	0	1	0

Source: Adapted from Diclectin® PSUR #4, Table 8, page 20.

Per the Diclectin® PSUR #5, covering the period February 1, 2010 to January 31, 2011, "During the reference period, three (3) reports involving infants who had been exposed to Diclectin® *in utero* were received, one (1) of which was limb reduction defect as an event and death as an outcome, and the other two (2) which were associated with neonatal drug withdrawal syndrome." "There is no indication that doxylamine causes dependency. At this time, there is insufficient data to establish this as a possible side effect to the newborn."

Medical Officer's Comments:

Case CV344766 of limb reduction defect was reported by a physician to Canada Vigilance. According to the case details, in addition to Diclectin®, the patient used Cipralex® (escitalopram) and Tamiflu® (oseltamivir) all of unknown dosing, frequency of administration and therapy dates. No further information is provided.

The 2 cases of neonatal withdrawal syndrome include:

1. *"Case CV353262 (DUC2010-1129): male infant of 6 months who demonstrated irritability exposed to Diclectin® in utero. The mother had taken Diclectin® (4 tablets daily) for 7 months throughout her pregnancy. Per the Applicant, "Based on the Diclectin® Product Monograph, Diclectin® is approved at a maximum dosage of four (4) tablets daily. Diclectin® has been shown to be safe and effective and can be prescribed in any trimester of pregnancy. Based on available safety data, there is no information to indicate that abuse or dependency occurs with the concentration of doxylamine succinate and pyridoxine HCL found in Diclectin®. Although unlikely related given the duration of the effect, an association between the reported reactions and Diclectin® can not entirely be excluded."*
2. *"Case CV359013 reported by a healthcare professional to Canada Vigilance involved a mother-child report where the neonate developed drug withdrawal syndrome after being exposed to Diclectin® in utero. "Co-suspect medications included Celexa, Clomid, Cyclobenzaprine, Imovane, Lidocaine, Naloxone, Oxycontin and Tramacet. The strengths, administration frequencies and duration of treatment with these products were unspecified except for Oxycontin which was 30 mg q.d. The outcome for this case was unknown."*

This reviewer concurs that insufficient information is provided to establish causality in these reported cases.

In PSUR #5, the cumulative total number under the SOC: Congenital, Familial and Genetic Disorders increased to 13 (Total=13) with the addition of the 1 case discussed above. One (1) case of fetal hypokinesia was added (Total=7) to the SOC: Pregnancy, Puerperium and Perinatal Conditions.

In addition, the following case of interest is reported in the Diclectin® PSUR #5: "During the reference period, one (1) case (DUC2010-22) of exposure through breast milk was reported by a female customer. According to the report, the customer's nine (9) month old daughter experienced somnolence (sleeping six to eight hours at a time) after the nursing mother switched from one (1) Diclectin® tablet at night to two (2) tablets at night. Prescribing Diclectin® for use during lactation is considered off-label. As case reports of this kind are currently limited, no conclusions can be drawn at this time. Such case reports will however continue to be closely monitored to determine possible effects on breastfeeding infants."

Medical Officer's Comments:

This reviewer concurs with the Applicant that doxylamine/pyridoxine exposure through breast milk should continue to be closely monitored to determine possible effects on breastfeeding infants.

Per the Diclectin® PSUR #6 covering the period February 1, 2011 to January 31, 2012, "the Diclectin® manufactured and sold in Canada is not sourced to other countries with the exception of Barbados and Antigua from which no adverse events reports were received during the period." "During the current reporting period, the approximate number of patients who received Diclectin® was estimated from sales data as (b) (4) women."

In the Diclectin® PSUR #6, the cumulative total number under the SOC: Congenital, Familial and Genetic Disorders increased to 15 (Total=15) with the addition of 1 case of cerebral ventricle dilatation and 1 case of holoprosencephaly. One (1) case of spontaneous abortion was added (Total=8) to the SOC: Pregnancy, Puerperium and Perinatal Conditions.

Medical officer's Comments:

Overall, there has been vast clinical experience using the combination of doxylamine and pyridoxine, with or without dicyclomine hydrochloride, in pregnant women. The background baseline risk of major malformations for all pregnancies is approximately 1 to 3%. This is the background risk of having a child with a birth defect when no drugs or chemicals are taken during pregnancy. This underlying risk may be increased due to maternal age, medical or family history, or exposures to certain drugs, chemicals or levels of radiation known to cause birth defects.

In 1979, the FDA developed a system for rating drug safety in pregnancy to provide therapeutic guidance. The FDA rating system was acknowledged to have important limitation, and in 2008 the FDA removed the A to X rating categories. Currently, however, the A to X rating categories are appearing in product labeling. The FDA categories for drugs and medications are:

***"Category A:** Studies in pregnant women have not shown an increased risk for fetal abnormalities if administered during the first (second, third, or all) trimester(s) of pregnancy, and the possibility of fetal harm appears remote. Fewer than 1 percent of all medications are in this category. Examples include levothyroxine, potassium supplementation, and prenatal vitamins, when taken at recommended doses."*

***"Category B:** Animal reproductive studies have been performed and have revealed no evidence of impaired fertility or harm to the fetus. Prescribing information should specify kind of animal and how dose compares with human dose.*

or

Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy, and there is no evidence of risk in later trimesters. Examples include many antibiotics, such as penicillins, macrolides, and most cephalosporins."

*"**Category C:** Animal reproduction studies have shown that this medication is teratogenic (or embryocidal or has other adverse effect), and there are no adequate and well-controlled studies in pregnant women. Prescribing information should specify kind of animal and how dose compares with human dose.*

or

There are no animal reproduction studies and no adequate and well-controlled studies in humans.

Approximately two thirds of all medications are in this category. It contains medications commonly used to treat potentially life-threatening medical conditions, such as albuterol for asthma, zidovudine and lamivudine for human immunodeficiency viral infection, and many antihypertensives, including β-blockers and calcium-channel blockers."

*"**Category D:** This medication can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy or if a woman becomes pregnant while taking this medication, she should be apprised of the potential hazard to the fetus.*

This category also contains medications used to treat potentially life-threatening medical conditions, for example: systemic corticosteroids, azathioprine, phenytoin, carbamazepine, valproic acid, and lithium."

*"**Category X:** This medication is contraindicated in women who are or may become pregnant. It may cause fetal harm. If this drug is used during pregnancy or id a woman*

becomes pregnant while taking this medication, she should be apprised of the potential harm to the fetus.

There are a few medications in this category that have never been shown to cause fetal harm but should be avoided nonetheless such as the rubella vaccine."

Overall, the postmarketing experience since 1983 with Diclectin® 10 mg doxylamine and 10 mg pyridoxine) and the published literature shows that the combination of 10 mg doxylamine and 10 mg pyridoxine use in early pregnancy to treat NVP does not increase a woman's baseline risk of having a child with a major malformation.

9 Appendices

9.1 Literature Review/References

The application includes a large amount of scientific literature related to the combination of doxylamine and pyridoxine, with and without dicyclomine HCL. This reviewer did not find a need to conduct an extensive search of additional literature, except where specific articles referenced an associated publication that was of particular interest.

9.2 Labeling Recommendations

This reviewer recommends the approval of Diclegis for the treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management once the DRUP final agreed upon labeling with the Applicant has been approved by the Division of Medical Policy (DMPP), the Office of Prescription Drug Promotion, (OPDP), the Division of Consumer Drug Promotion (DCPD), and formatting deficiencies have been corrected.

9.3 Advisory Committee Meeting

No advisory committee was needed or conducted for NDA 21876.

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/s/

THERESA H VAN DER VLUGT
03/13/2013

SHELLEY R SLAUGHTER
03/13/2013
I concur with Dr. van der Vlugt's conclusions and recommendations